



US009226960B2

(12) **United States Patent**
Bush

(10) **Patent No.:** US 9,226,960 B2
(45) **Date of Patent:** Jan. 5, 2016

(54) **FGF MODULATION OF IN VIVO ANTIBODY PRODUCTION AND HUMORAL IMMUNITY**

(71) Applicant: **Andrew B. Bush**, Princeton, NJ (US)

(72) Inventor: **Andrew B. Bush**, Princeton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 244 days.

(21) Appl. No.: **13/888,124**

(22) Filed: **May 6, 2013**

(65) **Prior Publication Data**

US 2013/0236483 A1 Sep. 12, 2013

Related U.S. Application Data

(63) Continuation-in-part of application No. 12/941,070, filed on Nov. 7, 2010, now Pat. No. 8,435,525.

(60) Provisional application No. 61/324,947, filed on Apr. 16, 2010.

(51) **Int. Cl.**

A61K 39/39 (2006.01)
A61K 45/00 (2006.01)
C07K 14/50 (2006.01)
C07K 16/00 (2006.01)

(52) **U.S. Cl.**

CPC *A61K 39/39* (2013.01); *A61K 45/00* (2013.01); *C07K 14/503* (2013.01); *C07K 16/00* (2013.01)

(58) **Field of Classification Search**

CPC A61K 39/39
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,994,559 A	2/1991	Moscatelli et al.
5,229,501 A	7/1993	Keifer et al.
5,288,855 A	2/1994	Bergonzoni et al.
5,440,021 A	8/1995	Chuntharapai et al.
5,530,101 A	6/1996	Queen et al.
5,707,632 A	1/1998	Williams et al.
5,891,655 A	4/1999	Ornitz
5,990,088 A	11/1999	Ensoli et al.
6,071,885 A	6/2000	Florkiewicz et al.
6,255,454 B1	7/2001	Keifer et al.
6,350,593 B1	2/2002	Williams et al.
6,900,053 B2	5/2005	Freier
2012/0214740 A1	8/2012	Imamura et al.

FOREIGN PATENT DOCUMENTS

WO WO 03/072603 A2 9/2003
WO WO 2007/080325 A1 7/2007

OTHER PUBLICATIONS

Jain, V.K., et al. "Challenges and opportunities in the targeting of fibroblast growth factor receptors in breast cancer." *Breast Cancer Research*. (2012), vol. 14:208, pp. 1-9.*

Abraham et al., 1986. *Human basic fibroblast growth factor: nucleotide sequence and genomic organization*. *Embo J* 5:2523.

Bai et al., *GP369, an FGFR2-IIIb-specific antibody, exhibits potent antitumor activity against human cancers driven by activated FGFR2 signaling*. *Cancer Res* 2010; 70 (19) 7630-9.

Brasile et al., *Bioengineered skin allografts: a new method to prevent humoral response*. *ASAO Journal* May-Jun. 2011; 57(3): 239-243.

Brunner et al., 1993. *Basic fibroblast growth factor expression in human bone marrow and peripheral blood cells*. *Blood* 81:631.

Bryant et al., *Vascular remodeling in response to altered blood flow is mediated by fibroblast growth factor-2*. *Circ Res*, 1999, 84 (3) 323-8.

Camozzi et al., *Pentraxin 3 inhibits fibroblast growth factor 2-dependent activation of smooth muscle cells in vitro and neointima formation in vivo*. *Arterioscler Thromb Vasc Biol*. Sep. 2005; 25(9):1837-42. *Epub Jul. 14, 2005*.

Chesi et al., *Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3*. *Nature Genetics*, 1997, 16 (3) 260-4.

Chou et al., 2003. *Bone marrow immunohistochemical studies of angiogenic cytokines and their receptors in myelofibrosis with myeloid metaplasia*. *Leuk Res* 27:499.

Coffin et al., 1995. *Abnormal bone growth and selective translational regulation in basic fibroblast growth factor (FGF-2) transgenic mice*. *Mol Biol Cell* 6:1861.

Dono et al., 1998. *Impaired cerebral cortex development and blood pressure regulation in FGF-2-deficient mice*. *Embo J* 17:4213.

Dutt et al., *Drug-sensitive FGFR2 mutations in endometrial carcinoma*. *Proc Natl Acad Sci U S A*. Jun. 24, 2008; 105(25):8713-7.

Fagarasan et al., 2000. *T-Independent immune response: new aspects of B cell biology*. *Science* 290:89.

Firme et al., *FGF signaling inhibits the proliferation of human myeloma cells and reduces c-myc expression*. *BMC Cell Biol*. Dec. 4, 2003;4:17.

Gavine et al., *AZD4547: an orally bioavailable, potent, and selective inhibitor of the fibroblast growth factor receptor tyrosine kinase family*, *Cancer Res*. Apr. 15, 2012; 72(8):2045-56. doi: 10.1158/0008-0437.CAN-11-3034. *Epub Feb. 27, 2012*.

Guagnano et al., *Discovery of 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-[6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl]-1-methyl-urea (NVP-BGJ398), a potent and selective inhibitor of the fibroblast growth factor receptor family of receptor tyrosine kinase*. *J Med Chem*. 2011, 54 (20) 7066-83.

Guagnano et al., *FGFR genetic alterations predict for sensitivity to NVP-BGJ398, a selective pan-FGFR inhibitor*. *Cancer Discov*. Sep. 20, 2012, CD-12-0210, Published Online.

Gozgit et al., *Ponatinib (AP24534), a multitargeted pan-FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models*, *Mol Cancer Ther* 2012, 10(1): 126-137.

Harding et al., *Preclinical efficacy of FP-1039 (FGFR1:Fc) in endometrial carcinoma models with activating mutations in FGFR2*. 101st Annual Meeting of the American Association for Cancer Research. abstr. 2597, Apr. 17, 2010.

Hori et al., *Suppression of solid tumor growth by immunoneutralizing monoclonal antibody against human basic fibroblast growth factor*. *Cancer Res*, 1991, 51 (22) 6180-4.

(Continued)

Primary Examiner — Noble Jarrell

Assistant Examiner — John S Kenyon

(74) Attorney, Agent, or Firm — Paul Diamond, Esq.; Diamond Law Office, LLC

(57)

ABSTRACT

The invention provides methods for increasing or decreasing antibody production in vivo by inhibiting or promoting the activity of fibroblast growth factor-2 (FGF2) respectively.

13 Claims, 3 Drawing Sheets

(56)

References Cited**OTHER PUBLICATIONS**

- Karrer et al., 2000. *Antiviral B cell memory in the absence of mature follicular dendritic cell networks and classical germinal centers in TNFR1-/- mice.* J Immunol 164:768.
- Keer et al. *Enrolling a rare patient population: Establishing proof of concept for FP-1039, an FGF “trap,” in endometrial cancer patients with the S252W FGFR2 mutation.* J Clin Oncol 28: 15s, 2010, ASCO Annual Meeting 2010, Abstract TPS260.
- Lee et al., *Antibody-producing capacity in human cancer.* Br J Cancer. Sep. 1970;24(3):454-63.
- MacLennan et al., 2003. *Extrafollicular antibody responses.* Immunol Rev 194:8.
- Martin et al., 2001. *Marginal zone and B1 B cells unite in the early response against T-independent blood-borne particulate antigens.* Immunity 14:617.
- Miller et al., 2000. *Compensation by fibroblast growth factor 1 (FGF1) does not account for the mild phenotypic defects observed in FGF2 null mice.* Mol Cell Biol 20:2260.
- Ornitz et al., 1996. *Receptor specificity of the fibroblast growth factor family.* J Biol Chem 271:15292.
- Ornitz et al., 2001. *Fibroblast growth factors.* Genome Biol 2.
- Ortega et al., 1998. *Neuronal defects and delayed wound healing in mice lacking fibroblast growth factor 2.* Proc Natl Acad Sci U S A 95:5672.
- Pasparakis et al., 1996. *Immune and inflammatory responses in TNF alpha-deficient mice: a critical requirement for TNF alpha in the formation of primary B cell follicles, follicular dendritic cell networks and germinal centers, and in the maturation of the humoral immune response.* J Exp Med 184:1397.
- Qing et al., *Antibody-based targeting of FGFR3 in bladder carcinoma and t(4;14)-positive multiple myeloma in mice.* J Clin Invest. May 2009;119(5):1216-29.
- Ravetch et al., 2000. *Immune inhibitory receptors.* Science 290:84.
- Salzer et al. *Common variable immunodeficiency (CVID): exploring the multiple dimensions of a heterogeneous disease.* Ann N Y Acad Sci. Feb. 2012;1250:41-9. Epub Feb. 2, 2012.
- Takai et al., 1996. *Augmented humoral and anaphylactic responses in Fc gamma RII-deficient mice.* Nature 379:346.
- Takeuchi et al., 1999. *Differential roles of TLR2 and TLR4 in recognition of gram-negative and gram-positive bacterial cell wall components.* Immunity 11:443.
- Tolcher et al., 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Nov. 16-19, 2010 Berlin, Germany. *Preliminary Results of a Dose Escalation Study of the FGF “trap” FP-1039 (FGFR1:Fc) in Patients with Advanced Malignancies.*
- Trudel et al., *The inhibitory anti-FGFR3 antibody, PRO-001, is cytotoxic to t(4;14) multiple myeloma cells.* Blood. May 15, 2006;107(10):4039-46.
- Wang et al., *A novel monoclonal antibody to fibroblast growth factor 2 effectively inhibits growth of hepatocellular carcinoma xenografts.* Mol Cancer Ther. Apr. 2012;11(4):864-72.
- Wiedemann et al., 2000. *Characterization of a novel protein (FGFRL1) from human cartilage related to FGF receptors.* Genomics 69:275.
- Yang et al., 1998. *Toll-like receptor-2 mediates lipopolysaccharide-induced cellular signalling.* Nature 395:284.
- Zhou et al., 1998. *Fibroblast growth factor 2 control of vascular tone.* Nature Medicine 4:201.
- Immunologic Deficiency Syndromes, in MeSH Database, National Center for Biotechnology Information, Bethesda, MD, USA [online], [retrieved on May 20, 2014]. Retrieved from the Internet: <URL: <http://www.ncbi.nlm.nih.gov/mesh/68007153>>.
- Severe Combined Immunodeficiency, in MeSH Database, NCBI, Bethesda, MD, USA [online], [retrieved on Feb. 27, 2015]. Retrieved from the Internet: <URL: <http://www.ncbi.nlm.nih.gov/mesh/68016511>>.

* cited by examiner

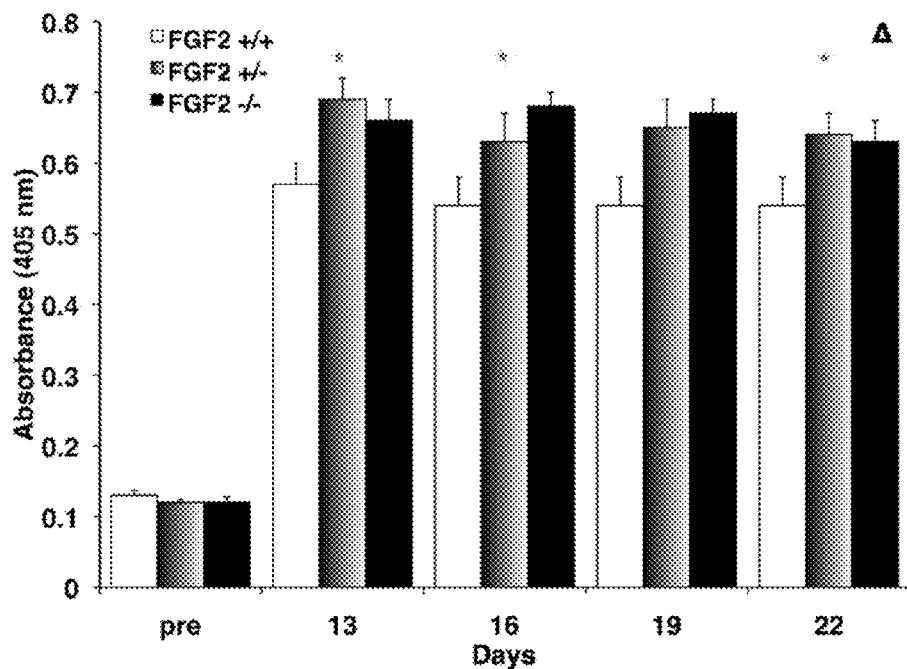


FIG. 1A

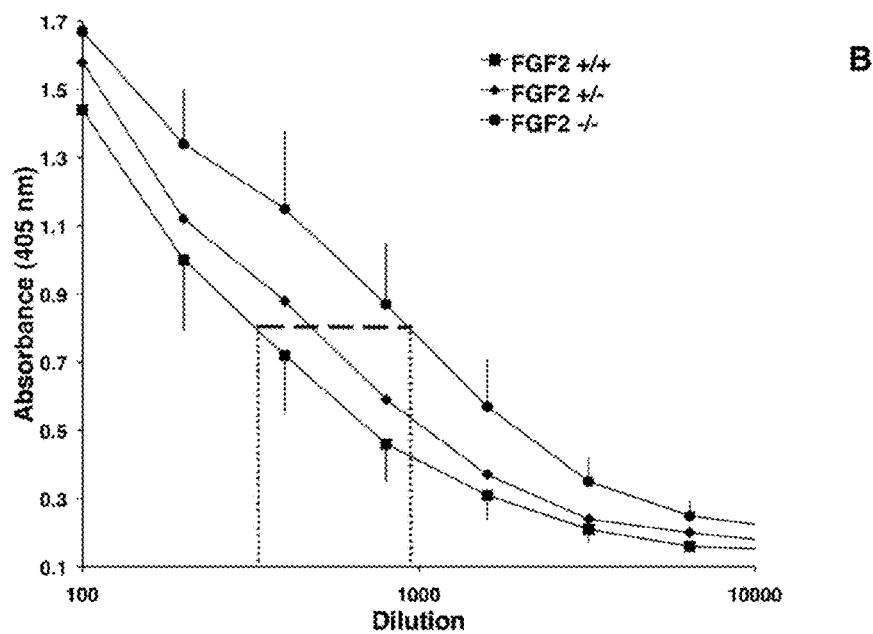


FIG. 1B

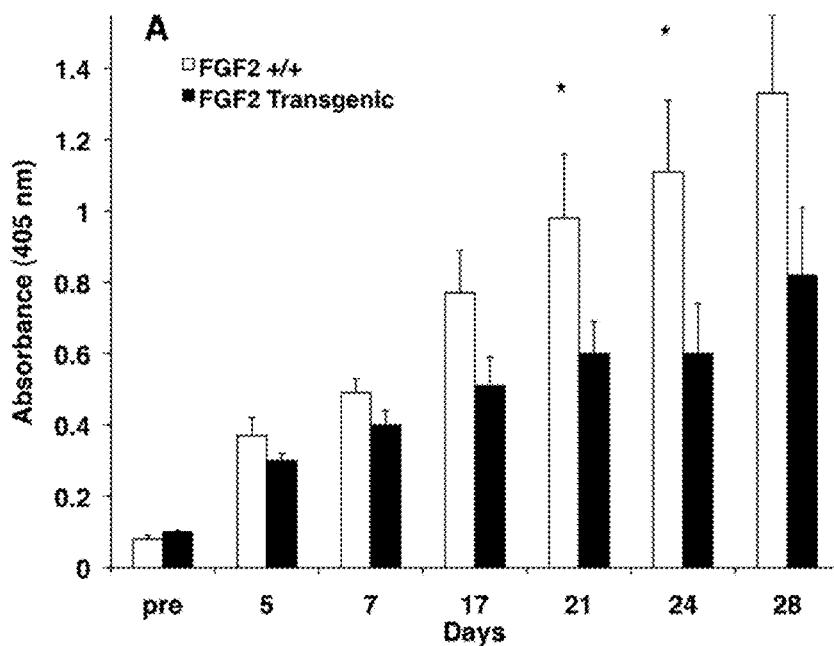


FIG. 2A

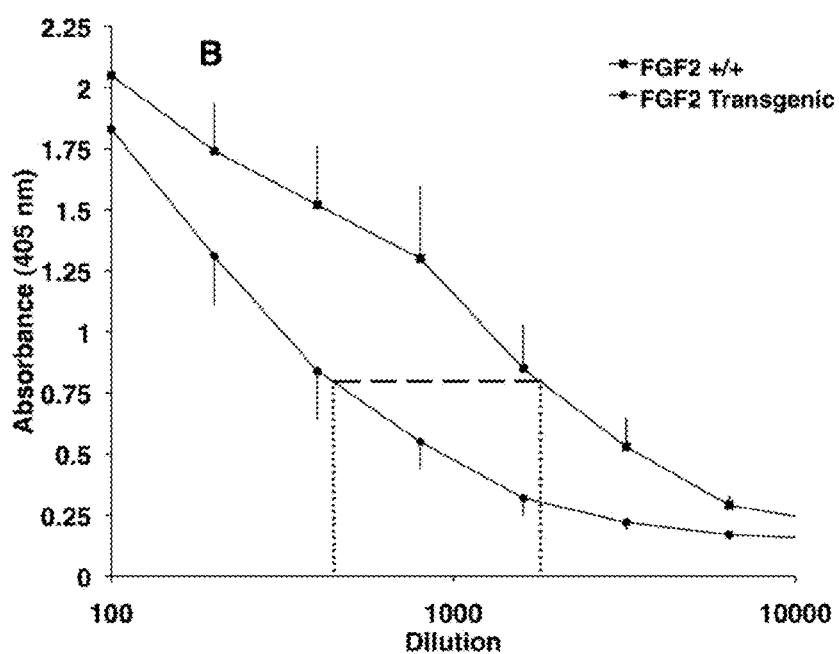


FIG. 2B

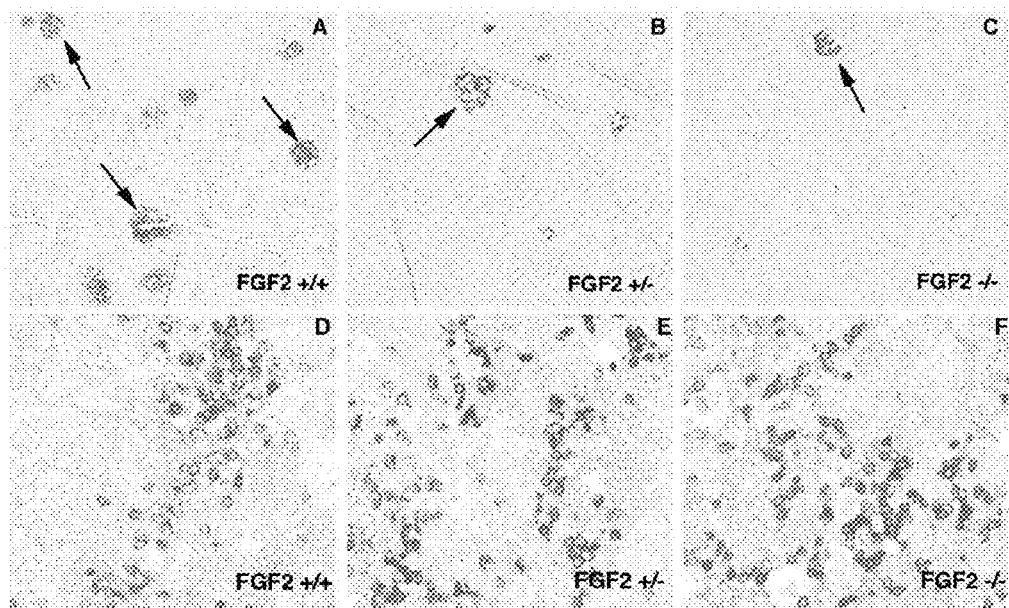


FIG. 3

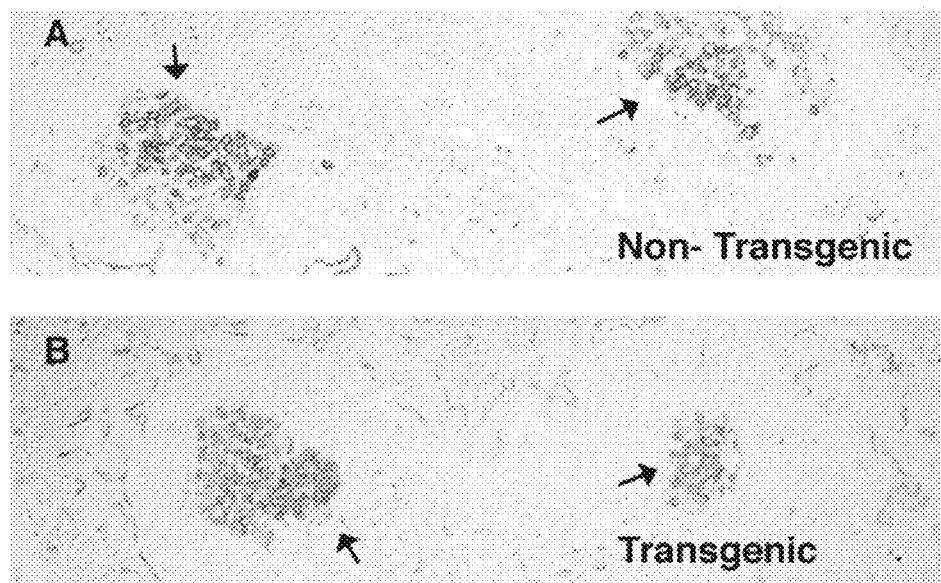


FIG. 4

1**FGF MODULATION OF IN VIVO ANTIBODY PRODUCTION AND HUMORAL IMMUNITY****CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a continuation-in-part of U.S. patent application Ser. No. 12/941,070 filed Nov. 7, 2010 (now U.S. Pat. No. 8,435,525) which claims the benefit of U.S. provisional patent application Ser. No. 61/324,947 filed Apr. 16, 2010, each of which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 3, 2013, is named AB001D1Sq.txt and is 275,405 bytes in size.

FIELD OF THE INVENTION

The invention relates to the field of humoral immunity.

BACKGROUND OF INVENTION

Organisms control antibody production at multiple steps during an immune response and this response must be carefully adjusted to the invading pathogen. If the response is excessive, autoimmune defects can damage host tissues, whereas if it is inadequate, the pathogen may persist and threaten survival. Soluble factors have been identified that stimulate the humoral immune response, but our knowledge of negative regulators of this process has been quite limited (Ravetch et al., 2000, *Science* 290:84). Indeed, few soluble cytokines have been identified whose loss of function leads to enhanced antibody production.

During the humoral immune response, a complex set of signaling events orchestrate antibody production. The process begins with antigen presentation to mature peripheral B cells, which proliferate and migrate to germinal centers. Cells possessing B cell receptors with the highest affinity for antigen are favored to survive while their low-affinity counterparts more readily undergo apoptosis. The activated B cells which survive this selection differentiate into memory B cells or antibody-secreting plasma cells. Many B cells also secrete antibody outside of the germinal center selection process in the extrafollicular response (MacLennan et al., 2003, *Immunol Rev* 194:8). Extrafollicular responses are thought to be important following exposure to T-independent antigens (Fagarasan et al., 2000, *Science* 290:89; Martin et al., 2001, *Immunity* 14:617). Once the antigen has been removed, B cells return to a resting state. Turning off B cell activation is necessary both for homeostatic resetting of antibody secretion and also for preventing pathologic autoimmune conditions. Little is known about the soluble factors which control the deactivation process.

The fibroblast growth factor (FGF) family of extracellular regulators has been shown to control the physiology and development of virtually all higher vertebrate tissues. Twenty-three FGF ligands have been identified in mammals, and these ligands interact with cell surface receptors encoded by five different genes (Wiedemann et al., 2000, *Genomics* 69:275; Ornitz et al., 2001, *Genome Biol* 2). Alternative splicing in the ligand-binding domain generates variable forms of the FGF receptors, thereby increasing diversity.

2

FGF2, or basic FGF, was the first identified FGF family member (Abraham et al., 1986, *Embo J* 5:2523) and is one of the most extensively studied. Expressed in most embryonic and adult tissues, it exists in high and low molecular weight isoforms due to initiation of translation at alternative start sites. It binds to all five receptors with preference for the "c" alternate splice form of receptors 1-3 (Ornitz et al, 1996, *J Biol Chem* 271:15292). FGF2 has been shown to stimulate widely varying effects, including proliferation, differentiation, apoptosis, and migration. Consequently, the FGF2 signal is interpreted differently depending on cellular context.

U.S. Pat. No. 4,994,559 discloses human basic fibroblast growth factor.

U.S. Pat. No. 5,229,501 discloses expression and use of human fibroblast growth factor receptor.

U.S. Pat. No. 5,228,855 discloses an extracellular form of human fibroblast growth factor receptor.

U.S. Pat. No. 5,707,632 discloses receptors for fibroblast growth factors.

U.S. Pat. No. 5,891,655 discloses methods for identifying molecules that regulate FGF activity and oligosaccharide modulators of FGF receptor activation.

U.S. Pat. No. 6,071,885 discloses treatment of FGF-mediated conditions by administration of cardiac glycoside and aglycone derivatives thereof.

U.S. Pat. No. 6,350,593 discloses receptors for fibroblast growth factors and methods for evaluating compositions for antagonism to fibroblast growth factors and fibroblast growth factors receptors.

U.S. Pat. No. 6,255,454 discloses expression and use of a human fibroblast growth receptor and a soluble version of the receptor.

U.S. Pat. No. 6,900,053 discloses antisense modulation of fibroblast growth factor receptor 2 expression.

Multiple human therapeutics are designed to enhance the immune response, but their use in humans are complicated by severe side effects. For example, exogenous IL-2 is administered to patients with advanced melanoma in order to stimulate the anti-tumor immune response. But this biologic, acting as a systemic cytokine which directly activates T cells, is beset by harsh side effects, such as dangerous hypotension. What is needed are new methods for enhancing immune function and, in particular, humoral immunity.

SUMMARY OF INVENTION

A new role for fibroblast growth factor (FGF) signaling in the negative regulation of the humoral immune response has been discovered by the present inventor. It has been found that antibody production to a Type I Independent antigen is enhanced in the absence of FGF2 and conversely, is suppressed when FGF2 is over-expressed. Therefore, FGF2 is an inhibitor of the humoral immune response. In addition, it has been discovered that splenic germinal centers require FGF2 for efficient formation.

One embodiment of the invention provides a method for increasing humoral immune response to vaccination with an immunogen, for example, an antigen or a live or killed vaccine, in a mammal or other higher vertebrate, that includes: in conjunction with the vaccination of a mammal to the immunogen other than FGF2, inhibiting the activity of a fibroblast growth factor, such as FGF2, in the mammal, thereby increasing the humoral immune response to the antigen. In one variation, the immunogen is other than a fibroblast growth factor and other than a fibroblast growth factor receptor.

Another embodiment of the invention provides a method for treating an immune deficiency in a mammal, such as a

human, that includes: increasing the production of endogenous antibodies in the mammal by inhibiting the activity of a fibroblast growth factor, such as FGF2, in the mammal.

A further embodiment of the invention provides a method for treating a microbial infection in a mammal, such as a human, that includes: inhibiting the activity of a fibroblast growth factor, such as FGF2 in a mammal in need of treatment for a microbial infection, to an extent effective to increase antibody production in the mammal. The inhibiting step may include or consist of administering a fibroblast growth factor antagonist, such as a FGF2 antagonist, to the mammal in an amount effective to increase antibody production in the mammal. The method may further include the step of administering an antibiotic or anti-viral agent to the mammal which is active against the microbial infection.

Another embodiment of the invention provides a method for increasing in vivo antibody production in a mammal, such as a human, that does not have a cancer that includes the step of inhibiting the activity of a fibroblast growth factor, such as FGF2, in the mammal. In one variation, the mammal is a geriatric human.

A still further embodiment of the invention provides a method for decreasing antibody production, such as pathological antibody production, in a mammal such as a human, in need of such reduction, by administering to the mammal, in an amount effective to decrease antibody production in the mammal, a fibroblast growth factor or agonist thereof, such as FGF2 or an FGF2 agonist, or an agonist of a receptor that binds a fibroblast growth factor such as FGF2, for example FGFR1, FGFR2 and FGFR3.

Additional features, advantages, and embodiments of the invention may be set forth or apparent from consideration of the following detailed description, drawings, and claims. Moreover, it is to be understood that both the foregoing summary of the invention and the following detailed description are exemplary and intended to provide further explanation without limiting the scope of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are included to provide a further understanding of the invention and are incorporated in and constitute a part of this specification, illustrate preferred embodiments of the invention and together with the detail description serve to explain the principles of the invention.

FIG. 1A shows that FGF2 deficient mice respond more strongly to a Type I Thymus Independent Antigen.

FIG. 1B shows the difference in antibody titer of FGF2 deficient animals compared to littermate controls following immunization.

FIG. 2A shows FGF2 transgenic mice respond more weakly to a Type I Thymus Independent Antigen.

FIG. 2B shows the quantification of antibody titer of FGF2 transgenic animals compared to littermate controls following immunization.

FIG. 3, panels A-F, show that FGF2 deficiency affects germinal centers but not syndecan expression.

FIG. 4, panels A and B, show shows that ectopic expression of FGF2 does not suppress germinal center formation.

DETAILED DESCRIPTION

It is now shown that the humoral immune response is altered in FGF2 mutant mice. FGF2 deficient mice produce more antibody to a Type I independent antigen while FGF2 over-expressing mice show suppressed antibody production

to the same pathogenic stimulus. In addition, germinal center formation is compromised in the absence of FGF2. Surprisingly, changes in both antibody production and germinal center formation are observed in mice lacking a single copy of FGF2, demonstrating that lymphocytes are particularly sensitive to FGF2 gene dosage. These studies provide the first evidence that FGF signaling is a crucial regulator of the humoral immune response and mature B cell function.

Materials and Methods

Mice.

FGF2^{-/-} (homozygous gene knockout) mice were obtained from two academic sources. These mice display relatively benign defects in wound healing, blood pressure regulation and cortical neurogenesis and do not express detectable levels of FGF2 protein (Ortega et al., 1998, Proc Natl Acad Sci USA 95:5672; Zhou et al., 1998, Nature Medicine 4:20). Both sets of knockouts showed increases in antibody production and data in FIGS. 1 and 3 are for animals obtained from the University of Cincinnati. Heterozygous animals (mixture of 129SvEv:Black Swiss) were mated and heterozygous and null animals were compared to littermate controls. Adult mice of both sexes were used. FGF2 transgenic animals exhibit bone dysplasia and disruption of endothelial homeostasis (Fulgham et al., 1999, Endothelium 6:185; Coffin et al., 1995, Mol Biol Cell 6:1861). Animals (FVB/N) heterozygous for the transgene were mated to wild type and adult animals of both sexes were compared to littermate controls. Animals were maintained in a pathogen-free facility, following institutional standards. Protocols adhered to IACUC guidelines.

Humoral Immune Response.

Mice were immunized intraperitoneally with 50 ug TNP-LPS (tri-nitrophenol lipopolysaccharide) emulsified with complete Freund's adjuvant in PBS (200 ul final volume). Serum was harvested from retro-orbital eye bleeds. After coagulation, bleeds were centrifuged and sodium azide (0.01%) was added. ELISAs for TNP specific antisera were performed on plates coated with TNP-BSA (Biosearch) and primary antisera were bound overnight at 4° C. Goat anti-mouse IgG (all Ig isotypes) coupled to Alkaline Phosphatase was used as secondary antisera (Jackson). The genotype of the serum was unknown to the experimenter. Absorbance (405 nM) was measured in triplicate on a Molecular Devices spectrophotometer. Values were averaged and measurements were taken from absorbance in the middle of the dynamic range. For quantification of difference in antibody titer, serial dilutions were performed and the average value from the serum of all animals (minimum n=5, +/- s.e.m.) was plotted. Omission of either primary or secondary antisera reduced signal to background levels.

Immunohistochemistry

Histochemistry was performed on 5 micrometer histologic sections made from formalin fixed, paraffin-embedded spleens. Sections were blocked in PBST (PBS with 0.1% Tween-20) containing 10% normal rabbit serum, stained with the lectin peanut agglutinin, then biotinylated anti-peanut agglutinin (Vector Laboratories, Burlingame, Calif.), or rat anti-CD138 (syndecan-1) (Becton Dickinson) followed by biotinylated goat anti-rat IgG secondary antibody (Jackson Immunoresearch). Primary antibody was incubated either overnight at 4° C. or for one hour at room temperature. Removal of either primary or secondary antiserum abolished specific signal.

Germinal center number was scored by experimenters blind to the source of the sections. At least three serial sections were scored for each spleen. Results are based on three inde-

pendent experiments from two or more animals per genotype. Data are presented from the final experiment which used the largest number of animals.

Proliferation of B Cells In Vitro.

Adult wild type mice (C57B16) were sacrificed and spleens were rapidly removed. After dissociation into single cell suspension and red blood cell lysis with NH4Cl, splenocytes were isolated by centrifugation over a Ficoll gradient. Subsequently, B lymphocytes were purified by one of two methods, complement mediated lysis or CD43 negative selection. For complement lysis, cells were incubated with anti-Thy 1 antibody (J1), anti-L3T4 (GK 1.5), anti-Ly2 (TIB105, ATCC) and rabbit complement (Sigma) for two hours at 37°. CD43 negative selection was carried out using anti-CD43 (Serotec) and Miltenyi microbeads according to the manufacturer's instructions. Cells were cultured in RPMI 1640, 10% fetal calf serum for three days in the presence of anti-CD40 (mAb 1C10, generous gift of Hsiou-Chi Liou, Weill Medical College of Cornell University) and anti-IgM Fab'2 fragments (Jackson ImmunoResearch). FGF1 (100 ng/ml) and Heparin (10 ug/ml) were added, and the number of cells was determined in triplicate compared to Heparin alone using a Coulter Counter (Coulter) or trypan blue exclusion with the same results.

Results

FGF2 Regulates the Humoral Immune Response

In the course of studies to evaluate the role of FGF signaling in multiple myeloma, we decided to investigate whether B cell function might be altered in FGF mutant mice. If FGF signaling affects mature B cell activity, one would predict that the humoral immune response would be affected by loss of function mutations in one of the FGF family members. To address this issue, we examined the humoral immune response in FGF2 deficient mice, one of the most widely expressed FGFs.

Immunization with a type I independent antigen, TNP-LPS, typically stimulates polyclonal B cell activation and proliferation. This antigen can elicit antibody production in T cell depleted animals, suggesting that the response can be largely independent of T cell help. The humoral response to TNP-LPS was enhanced in the absence of FGF2 (FIG. 1A). The magnitude of the peak response and the decay to baseline are potentiated by FGF2 deficiency. Three weeks after immunization, anti-TNP antibody titers are approximately three-fold higher than littermate controls (FIG. 1B). The size of this potentiation is greater than that seen with the inhibitory FC receptor, FC γ RIIB, a gene intrinsic to B cells (Takai et al., 1996, *Nature* 379:346). Surprisingly, mice lacking a single copy of FGF2 produce more anti-TNP antibody (FIG. 1A, day 13 and day 22 time point). These results demonstrate that FGF2 negatively regulates the primary humoral immune response and is required for the normal inactivation of antibody secretion.

FIG. 1.

55 FGF2 deficient mice respond more strongly to a Type I Thymus Independent Antigen. Mice were immunized with 50 ug TNP-LPS and anti-TNP specific antibodies were measured by ELISA. In FIG. 1A, data points represent average absorbance from the serum of at least five animals. Asterisks indicate statistical differences at p<0.05 (student's t test). FIG. 1B shows the quantification of the difference in antibody titer of FGF2 deficient animals compared to littermate controls at day nineteen after immunization. Data points represent the mean absorbance+/-s.e.m. at the indicated dilutions for each genotype. Broken line between curves with corresponding vertical line delineates difference in antibody titer at the same absorbance.

To determine whether FGF2 is sufficient to regulate antibody production, we examined the humoral immune response in FGF2 transgenic mice. These animals express a human FGF2 gene driven by the ubiquitously active promoter, phosphoglycerate kinase (Coffin et al., 1995, *Mol Biol Cell* 6:1861). Different forms of FGF2 protein are produced from the FGF2 gene, including several high and low molecular weight isoforms. In FGF2 transgenic animals, there is a marked increase in the expression of the 18-Kd form of FGF2 in selected tissues, including spleen (Coffin et al., 1995, *Mol Biol Cell* 6:1861).

FIG. 2.

15 FGF2 transgenic mice respond more weakly to a Type I Thymus Independent Antigen. Mice were immunized with 50 ug TNP-LPS and anti-TNP specific antibodies were measured by ELISA using TNP-BSA coated plates. Asterisks indicate statistical differences at p<0.05 (student's t test). FIG. 2B shows the quantification of antibody titer of FGF2 transgenic animals compared to littermate controls at day twenty one after immunization. Data points represent the mean absorbance+/-s.e.m. at the indicated dilutions. Broken line between curves with corresponding vertical line delineates difference in antibody titer at the same absorbance.

20 25 It was found that antibody production in response to TNP-LPS is significantly diminished in FGF2 transgenic animals, as shown in FIG. 2A. Suppression of antibody production begins relatively late during the primary response, with statistically significant differences not observable until twenty one days after administration of immunogen. The reduction in antibody titers is slightly larger than the enhancement seen in the absence of FGF2 (four-fold). Therefore, FGF2 is both necessary and sufficient to control the humoral immune response. Taken together, these observations identify FGF2 as a soluble regulator of antibody production.

30 35 Once activated by antigen, B cells migrate to germinal centers, where high affinity, somatically mutated antibodies are generated. To determine whether germinal centers are affected by FGF2, we examined the number of splenic germinal centers formed in the FGF2 null mice. Lectin staining reveals that the number of germinal centers is substantially reduced approximately two weeks after immunization with TNP-LPS, with six-fold fewer germinal centers formed in null animals (FIG. 3, panels a-c; Table 2). Fewer germinal centers are also observed two days after immunization (Table 1). Unexpectedly, germinal centers are also reduced in heterozygous animals.

TABLE 1

Mouse	+/-	+/-	-/-
1	4	2	1
2	3	0	0
3	0	0	0
4	8	0	0
5	3	2	—
6	1	2	—
7	0	1	—
8	0	4	—
9	1	0	—
10	4	0	—
11	4	3	—
12	3	3	—
13	—	4	—
Mean	2.6	1.6	0.25
s.e.m.	0.7	0.4	0.25
N	12	13	4

TABLE 2

Mouse	+/+	+/-	-/-
1	5	3	11
2	13	0	3
3	11	0	3
4	9	0	0
5	14	0	0
6	8	0.5	0
7	—	—	4
Mean	10	0.6	1.7
s.e.m.	1.4	0.5	0.76
N	6	6	7

Tables 1 and 2.

Germinal center formation is dependent on FGF2 gene dosage. FGF2^{+/+}, ^{+/−}, ^{−/−} mice were immunized i.p. with 50 µg TNP-LPS. Spleens were stained for expression of germinal centers with peanut agglutinin two days (Table 1) and approximately two weeks (Table 2) after immunization. Significantly fewer germinal centers were formed in FGF2 heterozygous ($p<0.01$) and null mice ($p<0.01$) sixteen days after immunization (Student's t test). Significantly fewer germinal centers were formed in FGF2 null mice ($p<0.05$) two days after immunization.

Gross morphologic features of the spleen are similar in the three genotypes. To determine whether plasma cell development is affected in FGF2 deficient animals, we examined the expression of syndecan-1, a cell surface heparin sulfate proteoglycan which is expressed on plasma cells. The number of syndecan positive plasma cells is not noticeably different, suggesting that FGF2 does not influence the adoption of the plasma cell fate in the spleen (FIG. 3, panels d-f). These results demonstrate that splenic germinal center formation is dependent on FGF2 gene dosage.

FIG. 3. FGF2 deficiency affects germinal centers but not syndecan expression. FGF2^{+/+}, ^{+/−}, ^{−/−} mice were immunized i.p. with 50 µg TNP-LPS. A-C) Spleens were stained for expression of germinal centers with peanut agglutinin two weeks after immunization. D-F) Expression of syndecan-1 was determined by monoclonal antibody anti-CD138 (BD).

TABLE 3

Mouse	Transgenic	Wild-type
1	3.5	6
2	2	6
3	0	2
4	0.5	0
5	2	2
6	3	4
7	0	1
8	2	2
9	4	8.5
10	2	—
Mean	1.9	3.5
s.e.m.	0.4	0.9
n	10	9

Table 3.

Germinal center formation is not affected by ectopic expression of FGF2. FGF2 transgenic mice and littermate controls were immunized i.p. with 50 µg TNP-LPS. Spleens were stained for expression of germinal centers with peanut agglutinin fourteen days after immunization.

To determine whether germinal centers were affected by over-expression of FGF2, we performed the same experiment in FGF2 transgenic animals. We find that although there is a trend towards fewer germinal centers when FGF2 is over-

expressed, the difference is not statistically significant (Table 3). These data show that over-expression of FGF2 is not sufficient to regulate germinal center formation two weeks after immunization with a Type 1 independent antigen.

FIG. 4.

Ectopic expression of FGF2 does not suppress germinal center formation. FGF2 transgenic and littermate controls were immunized i.p. with 50 µg TNP-LPS. A,B) Spleens were stained for expression of germinal centers with peanut agglutinin two weeks after immunization.

FGF2 is one of the more widely expressed members of the FGF family of ligands, with strong expression in multiple tissues. To determine whether FGF2 is expressed in the spleen we evaluated FGF2 levels by ELISA (R and D Systems). We find that FGF2 is found at 302 \pm 17 pg/ml (mean \pm s.e.d. n=4), demonstrating levels that are comparable to those found in other FGF2 responsive tissues. In addition, functional studies have demonstrated that both FGF-1 and FGF2 are present in the spleen in forms which can stimulate liver cell proliferation (Suzuki et al., 1992, Biochem Biophys Res Commun 186:1192).

To determine whether FGF can directly control B cell activation, we explored whether addition of exogenous FGF would affect B cell proliferation in vitro. B cells were purified from spleen and CD40 and BCR signaling were simultaneously activated using stimulating antibodies. Inducing these systems transmits powerful growth and survival signals, leading to rapid proliferation. To investigate whether FGF signaling might affect this response, we incubated the cells in the presence of FGF-1. We used FGF-1 instead of FGF2 because it stimulates the widest range of FGF receptors (8). Under these conditions, B cell number is inhibited by FGF stimulation (Table 3), suggesting that it can directly inhibit antigen stimulated B cells.

TABLE 4

	Experiment	% Decrease
40	1	27
	2	25
	3	10
	4	15
	5	16
	6	25
45	X	19.7 \pm 2.8

Table 4.

FGF signaling inhibits splenic B cell proliferation. Spleens from adult wild-type mice were dissected and highly enriched populations of B cells were purified. Cells were cultured in serum-containing medium for 3 days in the presence of a CD40 activating monoclonal antibody (1C10) and anti-mouse IgM Fab'2 fragments (Jackson). The values represent the percent decrease in total cell number observed with addition of 100 ng/ml FGF1 (determined in triplicate) as compared to heparin (10 µg/ml) alone. X=mean \pm s.e.m. One sample t test, p<0.01.

Discussion

Using gain and loss-of-function mouse models, it was shown that FGF2 controls the humoral immune response. These observations constitute the first indication that any member of this large family of pleiotropic signaling factors affects the humoral immune response.

Based on its widespread expression and its robust effects on a diverse array of cell types, FGF2 is postulated to control multiple biological processes. However, studies with mice lacking this gene have challenged this belief, implicating

other FGF family members or suggesting that FGF signaling is not essential (Ortega et al., 1998, Proc Natl Acad Sci USA 95:5672; Zhou et al., 1998, Nature Medicine 4:201; Dono et al., 1998, Embo J 17:4213). In light of these limited phenotypes, it was not expected that mice lacking a single copy of FGF2 would show abnormalities in immune function. Thus, in contrast to other systems, lymphoid tissue appears to be especially sensitive to FGF2 gene dosage. Since FGF family members are widely expressed, these results raise the possibility that further investigation will uncover additional evidence for FGF-dependent effects on lymphocyte function.

Given the ability of FGF ligands to bind more than one receptor family member, it is surprising that compensation for FGF2 deficiency by one of the twenty-two other FGFs was not observed. In this regard, FGF-1 constitutes a plausible candidate because it structurally resembles FGF2 and also is expressed in the spleen (Suzuki et al., 1992, Biochem Biophys Res Commun 186:1192). On the other hand, studies with FGF-1/2 double knock out mice suggest that the mild wound healing and neural phenotypes in FGF2 null mice are not a result of FGF-1 substituting for FGF2 (Miller et al., 2000, Mol Cell Biol 20:2260). The type I independent antigen lipopolysaccharide is a key pathogenic substance in the cell wall of gram negative bacteria. The repeating epitope in this molecule leads to massive engagement of receptors on the surface of B cells, including the BCR, TLR2 and TLR4 (Yang et al., 1998, Nature 395:284; Takeuchi et al., 1999, Immunity 11:443). B cell evolution has developed rapid and vigorous pre-existing defenses against such frequent threats and consequently, antibody secretion in response to this stimulus is robust. The greater response in the absence of FGF2 demonstrates that FGF2 negatively regulates the primary humoral immune response. The magnitude of the enhanced response is greater than the enhancement seen with FC receptor, FC \square RIIB, whose deletion shows no effect on the response to LPS at three weeks post immunization (Takai et al., 1996, Nature 379:346). It is believed that this represents the first example of enhanced antibody production in response to LPS due to genetic deficiency.

Animals over-expressing FGF2 have a suppressed humoral immune response to LPS, demonstrating that the gain of function phenotype is the opposite of the loss of function phenotype. It is concluded that FGF2 is both necessary and sufficient to regulate antibody production.

While not being limited by theory, it is not presently clear which step in the humoral immune response is inhibited by FGF2 signaling. Although the possibility that differences in plasma cell generation take place in other lymphoid tissues cannot be excluded, inhibition occurs without a substantial difference in the number of syndecan positive cells in the spleen (FIG. 3, panels D-F). Hence, FGF2 may regulate a step subsequent to the expression of syndecan-1, such as plasma-blast migration, full terminal differentiation, or metabolic function of antibody secreting cells in the bone marrow. Consistent with this latter idea, FGF2 is strongly expressed by multiple cell types in the bone marrow (Brunner et al., 1993, Blood 81:631; Chou et al., 2003, Leuk Res 27:499.).

FGF2 may control antibody production either by directly signaling to B cells or indirectly by affecting cells which regulate plasma cell activity. The direct model is consistent with our data showing decreased proliferation in response to FGF signaling of primary mature B lymphocytes (Table 3). While the reduction in cell number is modest, it should be borne in mind that few substances can overcome the strong growth and survival signals turned on by simultaneous CD40 and BCR engagement. In agreement with a direct mode of action, a previous study reported that FGF receptors exist on

normal human peripheral blood B cells (Genot, et al., 1989, Cell Immunol 122:424). However, the possibility that other cell types could mediate the observed effects cannot presently be excluded.

A negative correlation between antibody production and germinal center number was found. At first glance, this observation appears contradictory since one might expect that a reduction in germinal centers would decrease antibody production. However, numerous examples have demonstrated that germinal center number can be uncoupled from the humoral response. TNF receptor null animals lack germinal centers but produce substantial antibody titers in response to vesicular stomatitis virus (Karrer et al., 2000, J Immunol 164:768). Similarly, TNF- α null animals display dramatic alterations in splenic morphology but their antibody production to LPS is unaffected (Pasparakis et al., 1996, J Exp Med 184:1397).

Thus, the work described herein demonstrates that FGF2 plays two distinct and complementary roles in the humoral immune response. FGF2 facilitates germinal center formation, thereby contributing to the generation of activated B cells which defend against pathogenic stimuli. On the other hand, FGF2 reduces plasma cell activity and in so doing provides a limit on antibody production. Since FGF2 exerts opposing forces at different times during the B cell response, its activities in the immune system are certainly complex. Such complexity is consistent with observations in other tissues, where FGF signaling can stimulate radically different effects depending on its temporal and spatial locus of action.

Embodiments Relating to Inhibition of FGF2 Activity in a Mammal

In multiple disease states, vaccination provides inadequate protection and low percentages of seroconversion are observed (Cohen D et al., Diagnosis and management of the antiphospholipid syndrome. BMJ. 2010 May 14; 340:c2541). Non-limiting examples of vaccines for which the invention may be employed to increase humoral immune response include, Malaria vaccine (M. Esen et al. Vaccine. 2009 Nov. 16; 27(49):6862-8. Safety and immunogenicity of GMZ2—a MSP3-GLURP fusion protein malaria vaccine candidate); HIV vaccine (Hoxie J A. Annu Rev Med. 2010; 61:135-52. Toward an antibody-based HIV-1 vaccine.); Influenza vaccine (Nguyen M L et al Infect Immun. 2009 November; 77(11):4714-23. The major neutralizing antibody responses to recombinant anthrax lethal and edema factors are directed to non-cross-reactive epitopes); Influenza Vaccine in geriatric patients (Frasca D, Diaz, A, Romero, M et al. Vaccine. 2010 Oct. 22. Intrinsic defects in B cell response to seasonal influenza vaccination in elderly humans.); and Anthrax vaccine (Nguyen M L et al Infect Immun. 2009 November; 77(11): 4714-23. The major neutralizing antibody responses to recombinant anthrax lethal and edema factors are directed to non-cross-reactive epitopes.).

The invention may, for example, be used to increase antibody production and/or humoral immunity in patients, such as human patients, suffering from immunodeficiencies including but not limited to: Common variable immunodeficiency (Rezaei N et al Clin Vaccine Immunol. 2008 April; 15(4):607-11 Serum bactericidal antibody responses to meningococcal polysaccharide vaccination as a basis for clinical classification of common variable immunodeficiency.); primary immunodeficiency disorder (PIDD), Ig deficiency, IgG deficiency; and HIV disease (Acquired Immune Deficiency Syndrome).

11

One embodiment of the invention provides a method for increasing the humoral immune response to vaccination with an immunogen, for example, an antigen or a live vaccine, in a mammal, that includes: in conjunction with the vaccination of a mammal to the immunogen other than FGF2, inhibiting the activity of FGF2 in the mammal, thereby increasing the humoral immune response to the antigen. In one variation the immunogen is other than a fibroblast growth factor and other than a fibroblast growth factor receptor. The mammal may be a human, such as a geriatric human. The mammal, which may be human, may have an immune deficiency, such as but not limited to Common variable immunodeficiency; primary immunodeficiency disorder (PIDD), an immunoglobulin deficiency such as IgG deficiency, and HIV disease.

Another embodiment of the invention provides a method for treating an immune deficiency in a mammal, such as a human, that includes: increasing the production of endogenous antibodies in the mammal by inhibiting the activity of FGF2 in the mammal. In one variation, the mammal does not have cancer. The immune deficiency may be, for example, but is not limited to: Common variable immunodeficiency; primary immunodeficiency disorder (PIDD), an immunoglobulin deficiency such as IgG deficiency, and HIV disease. Non-human mammals also suffer from immunodeficiencies and may be treated according to the invention. For example, the method may be used to treat immunodeficiency associated with feline immunodeficiency virus (FIV) in a cat, such as a domesticated cat.

A further embodiment of the invention provides a method for treating a microbial infection in a mammal, such as a human, that includes: administering an FGF2 antagonist to a mammal in need of treatment for a microbial infection, wherein the FGF2 antagonist is administered in an amount effective to increase antibody production in the mammal. The method may further include the step of: administering an antibiotic or anti-viral agent to the mammal which is active against the microbial infection. The antibiotic or anti-viral agent is administered such that the effect of the antibiotic or anti-viral agent and that of the FGF2 antagonist are temporally overlapping in the mammal. The microbial infection may, for example, be a bacterial infection, a viral infection or a eukaryotic parasite infection. The method may further include the step of determining that the mammal has a microbial infection prior to administering the FGF2 antagonist.

Another embodiment of the invention provides a method for increasing *in vivo* antibody production in a mammal, such as a human, that does not have a cancer, which includes the step of inhibiting the activity of FGF2 in the mammal. In one variation, the mammal is a geriatric human or non-human mammal, such as a geriatric domesticated dog or cat.

A related embodiment provides a method for enhancing the production of antisera or polyclonal antibodies generally against a desired immunogen in a non-human mammal that includes the steps of: inhibiting FGF2 activity in the non-human mammal according to any of methods and ways described herein and immunizing the non-human mammal with an immunogen that is not a fibroblast growth factor or a fibroblast growth factor receptor, whereby the production of antibodies against the immunogen in the mammal is enhanced, increased and/or accelerated versus a comparable immunization without the inhibition of FGF2 activity. The method may further include the step of retrieving the polyclonal sera from the non-human mammal and optionally the step of isolating. The immunizing step may, for example, include more than one temporally separated immunization with the immunogen and may, for example, be aided by inclusion of an immunization adjuvant. The methods for pro-

12

duction of antisera and polyclonal antibodies are well known and long-established in the art. See, for example, U.S. Pat. No. 5,440,021.

The increase in antibody production in response to inhibition of FGF2 activity in a mammal is a general characteristic of the invention which is not limited to the type of FGF2 inhibitor that is administered to the mammal to inhibit the activity of FGF2. Preferred types of inhibitors of FGF2 activity include antibodies and binding fragments thereof, both 10 monoclonal and polyclonal, which bind to FGF2 and block its interaction with FGF binding receptors and antibodies, both monoclonal and polyclonal, which bind to an FGF receptor such as FGFR1, FGFR2 and FGFR3 and block binding of the ligand (FGF2) to the receptor. For example, a single chain, 15 monoclonal scFv antibody that neutralizes FGF2 may be used such as that described in Tao et al., Selection and characterization of a human neutralizing antibody to human fibroblast growth factor-2, *Biochem Biophys Res Commun.* 2010 Apr. 9; 394(3):767-73. Epub 2010 Mar. 17 or one obtained by the 20 method described therein. Antibodies blocking FGFR1 such as those described in Sun et al., *Am J Physiol Endocrinol Metab* 292:964-976, 2007, or obtained according to the method of this article may be used. Gorbenko et al, *Hybridoma*, Volume 28, Number 4, 2009 also describes the production 25 of anti-FGFR1 antibodies and their production. Monoclonal antibodies against FGFR3 and their production are described in Qing et al., *J. Clin. Invest.* 119:1216-1229 (2009) and in Gorbenko et al, *Hybridoma*, Volume 28, Number 4, 2009, 295-300.

Antibodies contain one or more antigen binding sites that specifically binds with an antigen. Antibodies include, but are not limited to polyclonal, monoclonal, chimeric, and humanized antibodies. Immunologically active portions include monovalent and divalent fragments such as Fv, single chain 30 Fv (scFv), single variable domain (sVD), Fab, Fab' and F(ab')2 fragments. Immunologically active portions can be incorporated into multivalent forms such as diabodies, triabodies, and the like. Antibodies further include antigen binding 35 fragments displayed on phage, and antibody conjugates.

An "isolated antibody" is an antibody that (1) has been partially, substantially, or fully purified from a mixture of components; (2) has been identified and separated and/or recovered from a component of its natural environment; (3) is monoclonal; (4) is free of other proteins from the same species; (5) is expressed by a cell from a different species; or (6) does not occur in nature. Isolated antibodies may, for example, be used as inhibitors of FGF2 activity according to the invention. Examples of isolated antibodies include an anti-FGF2 antibody that has been affinity purified using 40 FGF2, an anti-FGF2 antibody that has been made by a hybridoma or other cell line *in vitro*, a human anti-FGF2 antibody isolated from a library such as a phage library, and a human anti-FGF2 antibody derived from a transgenic mouse.

In general, naturally occurring antibody molecules are 45 composed of two identical heavy chains and two light chains. Each light chain is usually covalently linked to a heavy chain by an interchain disulfide bond, and the two heavy chains are further linked to one another by multiple disulfide bonds at the hinge region. The individual chains fold into domains 50 having similar sizes (about 110-125 amino acids) and structures, but different functions. The light chain comprises one variable domain (V_L) and one constant domain (C_L). The heavy chain comprises one variable domain (V_H) and, depending on the class or isotype of antibody, three or four 55 constant domains (C_H1 , C_H2 , C_H3 and C_H4). In mice and humans, the isotypes are IgA, IgD, IgE, IgG, and IgM, with IgA and IgG further subdivided into subclasses or subtypes.

13

The portion of an antibody consisting of V_L and V_H domains is designated "Fv" and constitutes the antigen-binding site. A single chain Fv (scFv) is an engineered protein containing a V_L domain and a V_H domain on one polypeptide chain, wherein the N terminus of one domain and the C terminus of the other domain are joined by a flexible linker. "Fab" refers to the portion of the antibody consisting of V_L - C_L (i.e., a light chain) and V_H - C_H1 (also designated "Fd").

Antibodies include without limitation single variable domains (sVDs) and antigen binding proteins that comprise sVDs. sVD binding sites can be obtained from antigen specific Fv regions (which comprise both V_H and V_L domains). Often, it can be shown that the binding affinity and specificity of an Fv region is contributed primarily by one of the variable domains. Alternatively, the scFv can be obtained directly. Direct sources of sVDs include mammals (e.g., camelids) that naturally express antibodies containing only V_H domain. Further, phage display libraries can be constructed to express only a single variable domain. For example, a human domain antibody phage display library is commercially available from Domantis (Cambridge, UK).

The antibody variable domains show considerable amino acid sequence variability from one antibody to the next, particularly at the location of the antigen binding site. Three regions, called "complementarity-determining regions" (CDRs) are found in each of V_L and V_H . The CDRs of an antibody are often referred to as "hypervariable regions."

"Fc" is the designation for the portion of an antibody which comprises paired heavy chain constant domains. In an IgG₁ antibody, for example, the Fc comprises C_H2 and C_H3 domains. The Fc of an IgA or an IgM antibody further comprises a C_H4 domain. The Fc is associated with Fc receptor binding, activation of complement-mediated cytotoxicity and antibody-dependent cellular-cytotoxicity. For natural antibodies such as IgA and IgM, which are complexes of multiple IgG like proteins, complex formation requires Fc constant domains.

Finally, the "hinge" region separates the Fab and Fc portions of the antibody, providing for mobility of Fabs relative to each other and relative to Fc, as well as including multiple disulfide bonds for covalent linkage of the two heavy chains. Thus, antibodies of the invention include, but are not limited to, naturally occurring antibodies, bivalent fragments such as (Fab')₂, monovalent fragments such as Fab, single chain antibodies, single chain Fv (scFv), single domain antibodies, multivalent single chain antibodies, diabodies, triabodies, and the like that bind specifically with antigens.

Antibody fragments also include polypeptides with amino acid sequences substantially similar to the amino acid sequence of the variable or hypervariable regions of the antibodies of the invention. Substantially the same amino acid sequence is defined herein as a sequence with at least 70%, at least about 80%, at least about 90%, at least about 95% or at least about 99% homology or identity to a compared amino acid sequence, as determined by the FASTA search method in accordance with Pearson and Lipman, Proc. Natl. Acad. Sci. USA 85:2444-2448 (1988).

Antibodies that may be employed as inhibitors according to the invention also include "chimeric" antibodies and binding fragments thereof. Such antibodies generally comprise variable domains of one antibody and constant domains of a different antibody. Typically, to minimize host immune responses against the antibody and to enhance host responses against the antibody target by retaining antibody effector functions, the constant domains of a chimeric antibody are taken from the same species to which the chimeric antibody will be administered.

14

Antibodies that may be employed as inhibitors according to the invention also include "humanized" antibodies. Humanized variable domains are constructed in which amino acid sequences which comprise one or more complementarity determining regions (CDRs) of non-human origin are grafted to human framework regions (FRs). For examples, see: Jones, P. T. et al., 1996, Nature 321, 522-25; Riechman, L. et al., 1988, Nature 332, 323-27; and U.S. Pat. No. 5,530,101 to Queen et al. A humanized construct is particularly valuable for elimination of adverse immunogenic characteristics, for example, where an antigen binding domain from a non-human source is desired to be used for treatment in a human. Variable domains have a high degree of structural homology, allowing easy identification of amino acid residues within variable domains which correspond to CDRs and FRs. See, e.g., Kabat, E. A., et al., 1991, Sequences of Proteins of Immunological Interest. 5th ed. National Center for Biotechnology Information, National Institutes of Health, Bethesda, Md. Thus, amino acids which are likely to participate directly in antigen binding are easily identified. In addition, methods have been developed to preserve or to enhance affinity for antigen of humanized binding domains comprising grafted CDRs. One way is to include in the recipient variable domain the foreign framework residues which influence the conformation of the CDR regions. A second way is to graft the foreign CDRs onto human variable domains with the closest homology to the foreign variable region. Queen, C. et al., 1989, Proc. Natl. Acad. Sci. USA 86, 10029-33. CDRs are most easily grafted onto different FRs by first amplifying individual FR sequences using overlapping primers which include desired CDR sequences, and joining the resulting gene segments in subsequent amplification reactions. Grafting of a CDR onto a different variable domain can further involve the substitution of amino acid residues which are adjacent to the CDR in the amino acid sequence or packed against the CDR in the folded variable domain structure which affect the conformation of the CDR. Humanized variable domains of the invention therefore include human domains which comprise one or more non-human CDRs as well as such domains in which additional substitutions or replacements have been made to preserve or enhance binding characteristics.

Antibodies with variable domains that have been made less immunogenic by replacing surface-exposed residues so as to make the antibody appear as self to the immune system may also be employed as inhibitors (Padlan, E. A., 1991, Mol. Immunol. 28, 489-98). Antibodies have been modified by this process with no loss of affinity (Roguska et al., 1994, Proc. Natl. Acad. Sci. USA 91, 969-973). Because the internal packing of amino acid residues in the vicinity of the antigen binding site remains unchanged, affinity is preserved. Substitution of surface-exposed residues according to the invention for the purpose of reduced immunogenicity does not mean substitution of CDR residues or adjacent residues which influence binding characteristics.

It is often preferable to employ variable domains that are essentially human as when the recipient of the antibody is human. Human antibodies comprise human V_H and V_L framework regions (FRs) as well as human complementary determining regions (CDRs). Preferably, the entire V_H and V_L variable domains are human or derived from human sequences. The antibodies can be obtained directly from human cells, for example by creating human hybridomas.

Alternatively, human antibodies can be obtained from transgenic animals into which unarranged human Ig gene segments have been introduced and in which the endogenous mouse Ig genes have been inactivated (reviewed in Briigge-

15

mann and Taussig, 1997, Curr. Opin. Biotechnol. 8, 455-58). Preferred transgenic animals contain very large contiguous Ig gene fragments that are over 1 Mb in size (Mendez et al., 1997, Nature Genet. 15, 146-56) but human Mabs of moderate affinity can be raised from transgenic animals containing smaller gene loci (See, e.g., Wagner et al., 1994, Eur. J. Immunol. 42, 2672-81; Green et al., 1994, Nature Genet. 7, 13-21).

Human antibodies can also be obtained from libraries of antibody V_H and/or V_L domains. For example, a variable domain library can be obtained from human genomic sequences, or from peripheral blood lymphocyte expressing productively rearranged variable region genes. Furthermore, the human gene library can be synthetic. In one embodiment, variable domain libraries can be created which comprise human framework regions with one or more CDRs that are synthesized to include random or partial random sequences. For example, a human V_H variable domain library can be created in which members are encoded by a human V_H gene segment and a synthetic sequence for the CDR3H region (i.e., a synthetic D_H - J_H gene segment). Likewise, a human V_L variable domain may be encoded by a human V_L gene segment and a synthetic sequence for the CDR3L region (i.e., a synthetic J_L gene segment). In another embodiment, the human frameworks may be synthetic in that they have a consensus sequence derived from known human antibody sequences or subgroups of human sequences. In another alternative, one or more CDRs is obtained by amplification from human lymphocytes expressing rearranged variable domains and then recombined into a particular human framework.

In order to screen libraries of variable domains, it is common to employ phage display libraries wherein combinations of human heavy and light chain variable domains are displayed on the surface of filamentous phage (see, e.g., McCafferty et al., 1990, Nature 348, 552-54; Aujame et al., 1997, Human Antibodies 8, 155-68). Combinations of variable domains are typically displayed on filamentous phage in the form of Fabs or scFvs. The library is screened for phage bearing combinations of variable domains having desired antigen binding characteristics. Preferred single domain and variable domain combinations display high affinity for a selected antigen and little cross-reactivity to other related antigens. By screening very large repertoires of antibody fragments, (see e.g., Griffiths et al., 1994, EMBO J. 13, 3245-60) a good diversity of high affinity binding domains are isolated, with many expected to have sub-nanomolar affinities for the desired antigen.

In a physiological immune response, mutation and selection of expressed antibody genes leads to the production of antibodies having high affinity for their target antigen. The V_H and V_L domains incorporated into antibodies of the invention can similarly be subject to in vitro or in vivo mutation and screening procedures in order to modify affinity and/or specificity. Thus, binding domains of the invention include those for which binding characteristics have been improved by mutating CDRs and/or FW regions by direct mutation, methods of affinity maturation, or chain shuffling. It is understood that amino acid residues that are primary determinants of binding of single domain antibodies can be within Kabat defined CDRs, but may include other residues as well. For sVDs, residues important for antigen binding can also potentially include amino acids that would otherwise be located at the interface of a V_H - V_L heterodimer. Typically, phage display is used to screen such mutants to identify those having the desired binding characteristics (see, e.g., Yang et al., J. Mol. Biol., 254: 392-403 (1995)). Mutations can be made in a variety of ways. One way is to randomize individual resi-

16

dues or combinations of residues so that in a population of otherwise identical sequences, all twenty amino acids or a subset thereof are found at particular positions. Alternatively, mutations may be induced over a range of CDR residues by error prone PCR methods (see, e.g., Hawkins et al., J. Mol. Biol., 226: 889-896 (1992)). For example, phage display vectors containing heavy and light chain variable region genes may be propagated in mutator strains of *E. coli* (see, e.g., Low et al., J. Mol. Biol., 250: 359-368 (1996)). These methods of mutagenesis are illustrative of the many methods known to one of skill in the art.

Inhibitors that may be used according to the invention also include antigen binding proteins engineered from non-immunoglobulin scaffolds. For example, affibodies, which are derived from an immunoglobulin-binding domain of *S. aureus* protein A, possess no disulfide bonds and display reversible folding. Another example is fibronectin, which has an antibody-like structure and displays CDR-like loops. In contrast to antibodies, the fibronectin domain structure does not rely on disulfide bonds, yet displays high thermodynamic stability. Binding sites can be engineered into such scaffolds by, for example, diversifying codons at specified positions and screening for binding to a desired antigen. Codons can be randomized in loops, flat surfaces, cavities, or combinations of such locations. Further, peptide sequences can be inserted, usually in loops. Target-binding variants of resulting libraries can be isolated using selection of screening techniques that are well known in the art, not limited to phage display, ribosome display, bacteria or yeast surface display, and the like.

For antigen-binding proteins intended for therapy, various strategies are available for minimizing potential immunogenicity. Human scaffolds can be employed, and immunogenicity can be minimized, for example, by PEGylation or T-cell epitope engineering (i.e., minimizing T-cell reactive sequences).

Antigen-binding proteins from non-immunoglobulin scaffolds often can be produced more economically than immunoglobulin-type proteins. For example, the absence of disulfide bonds or free cysteines allows for expression of functional molecules in the reducing environment of the bacterial cytoplasm, which usually gives higher yields than periplasmic expression, and is more convenient than refolding in vitro. Binz, H. K. et al. (Nat. Biotech. 23:1257-68, 2005) discloses a variety of such antigen-specific binding proteins and techniques for their development.

The identification or selection of antibodies or other molecules that inhibit binding of FGF2 or other FGFs to their receptors may be performed according to routine ligand-receptor binding assays, comparing binding in presence and absence of test agent, since the full sequences of FGF2 and its receptors are known in various mammals such as human. See, for example, U.S. Pat. No. 5,440,021 for ligand-receptor binding assays.

Another preferred type of inhibitor of FGF2 activity is a soluble FGF2-binding receptor or soluble portion of an FGF-binding receptor, such as a soluble form of FGFR1, FGFR2 and FGFR3. The soluble receptor sequence may, for example match the species in which it will be administered, i.e., a human receptor sequence may be used for a human recipient and so on. For example, FP-1039 is a soluble fusion protein consisting of the extracellular domains of human FGFR1 linked to the Fc region of human Immunoglobulin G1 (IgG1), which may be used as an FGF2 inhibitor/antagonist according to the invention (Five Prime Therapeutics, Inc., San Francisco, Calif.; Keer et al, ASCO 2010, Abstract no. TPS260).

FGF2 activity may also be inhibited according to the invention by vaccinating the subject mammal against FGF2 itself

or against FGFR1, FGFR2 and/or FGFR3. For example, a peptide vaccine targeting the heparin-binding portion of FGF2 can be used to generate a specific anti-FGF2 antibody response in a mammal according the method of Plum et. al., Generation of a specific immunological response to FGF2 does not affect wound healing or reproduction, Immunopharmacol Immunotoxicol. 2004 February; 26(1):29-41.

For embodiments in which a soluble polypeptide, such as an antibody or soluble receptor, is used to inhibit FGF2 activity, a composition for intravenous administration, for example, to a human, may include 0.1 to 20 mg, such as 0.1 to 10 mg, of the polypeptide, and this may be a daily dose. More generally, dosages from 0.1 mg to about 100 mg per subject per day for one or more days may be used. Methods for preparing administrable compositions are well known to those skilled in the art and are described in more detail in such publications as Remington's Pharmaceutical Science, 19th ed., Mack Publishing Company, Easton, Pa. (1995). Polypeptides for administration to a subject may, for example, be provided in lyophilized form and rehydrated with sterile water before administration. The solution of polypeptide may then be added to an infusion bag containing 0.9% sodium chloride, USP, and, for example administered at a dosage of from 0.5 to 15 mg/kg body weight. Alternatively, for example, the polypeptide can be administered as a bolus injection, for example, at a dosage of 0.5 to 30 mg/kg body weight.

Still other suitable types of FGF2 activity inhibitors include, for example, antisense oligonucleotides targeting FGF2 or one or more of FGFR1, FGFR2 and FGFR3. Still further suitable inhibitors are small molecule inhibitors, for example cardiac glycosides or aglycone derivatives as described in U.S. Pat. No. 6,071,885 and FGF activity modulating oligosaccharides as described in U.S. Pat. No. 5,891,655. TKI258 (also known as CHIR-258) described in Sarker et al., Clin Cancer Res, 2008; 14(7) 2075-81, is another suitable small molecule FGF receptor inhibitor. Brivanib, a FGFR1 Kinase inhibitor described in Bhide et al, Mol Cancer Ther; 9(2) February 2010, 369-78, is still another suitable small molecule inhibitor.

Embodiments Relating to Increasing FGF2 Activity in a Mammal

The invention also provides embodiments in which antibody production in vivo is purposefully reduced in a mammal, such as a human, by increasing FGF2 activity in the mammal, for example, by administration of FGF2 to the mammal or administration of an agonist of FGF2 or an agonist of an FGF2 receptor, such as FGFR1, FGFR2 or FGFR3 to the mammal, in an amount effective to decrease antibody production in the mammal. Where FGF2 is administered to a mammal recipient, the peptide sequence may, for example at least substantially or identically match the species in which it will be administered, i.e., a human receptor sequence may be used for a human recipient and so on.

This aspect of the invention finds practical application is the suppression of antibody production in acutely toxic states. In many cases, response to invading pathogens can lead to pathological autoimmune effects, with lymphocyte activity spiraling out of control. In situations like this, administration of FGF2 attenuates the uncontrolled secretion of antibody.

Similarly, multiple human pathologies result from secretion of autoimmune antibodies. Administration of FGF2 and FGF ligands will serve to attenuate the production of these antibodies and thus ameliorate the autoimmune disease. For example, autoimmune antibodies are observed in both sys-

temic lupus erythematosus (Cohen D et al., Diagnosis and management of the antiphospholipid syndrome. BMJ. 2010 May 14; 340:c2541) and diverse arthritic disease (Calero I, et al., B cell therapies for rheumatoid arthritis: beyond B cell depletion. Rheum Dis Clin North Am 2010 May; 36(2):325-43), including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis. In addition, increasing FGF2 activity in a mammal may be used to decrease or maintain a decreased level of antibody production in organ transplant patients, such as human organ transplant patients in order to decrease negative immune responses to and increase tolerance to the transplanted organ in the patient.

Accordingly, one embodiment of the invention provides a method for decreasing antibody production, such as pathological antibody production, in a mammal such as a human in need thereof by administering to the mammal FGF2 or an FGF2 agonist or an agonist of a receptor that binds FGF2 such as FGFR1, FGFR2 and FGFR3 in an amount effect to decrease antibody production in the mammal. In one variation, the mammal may have and be in need of treatment for systemic lupus erythematosus and diverse arthritic disease, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis and the method decreases the production of autoimmune antibodies in these mammals thereby treating the condition. In another variation, the mammal is an organ transplant patient such as a human organ transplant patient and the method reduces antibody response against the transplanted organ.

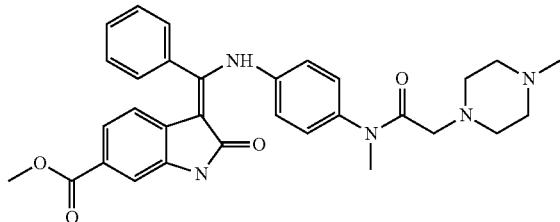
The sequences of fibroblast growth factors and their receptors are well characterized in humans and non-human mammals. For example, the following sequences are known and form part of this disclosure: Human FGF2 (NCBI Reference Sequence NM_002006.4; SEQ ID NO:1 peptide, SEQ ID NO:2 nucleotide), Human FGFR1 (GenBank Accession No. M34185.1; SEQ ID NO:3 peptide, SEQ ID NO:4 nucleotide), Human FGFR2 (NCBI Reference Sequence NM_000141.4; SEQ ID NO:5 peptide, SEQ ID NO:6 nucleotide), Human FGFR3 (NCBI Reference Sequence NM_000142.4; SEQ ID NO:7 peptide, SEQ ID NO:8 nucleotide), Human FGFR4 (GenBank Accession No. AF202063.1; SEQ ID NO:9 peptide, SEQ ID NO:10 nucleotide), *Bos taurus* FGF2 (NCBI Reference Sequence NM_174056.3; SEQ ID NO:11 peptide, SEQ ID NO:12 nucleotide), *Bos taurus* FGFR1 (Genbank Accession No. NM_001110207.1; SEQ ID NO:13 peptide, SEQ ID NO:14 nucleotide), *Bos taurus* FGFR2 (NCBI Reference Sequence XM_002698546.1; SEQ ID NO:15 peptide, SEQ ID NO:16 nucleotide); *Bos taurus* FGFR3 (NCBI Reference Sequence NM_174318.3; SEQ ID NO:17 peptide, SEQ ID NO:18 nucleotide), *Bos taurus* FGFR4 (NCBI Reference Sequence XM_002689008.1; SEQ ID NO:19 peptide, SEQ ID NO:20 nucleotide), *Sus scrofa* FGF2 (NCBI Reference Sequence XM_003129213.1; SEQ ID NO:21 peptide, SEQ ID NO:22 nucleotide), *Sus scrofa* FGFR1 (NCBI Reference Sequence: XM_001928678.2; SEQ ID NO:23 peptide, SEQ ID NO:24 nucleotide), *Sus scrofa* FGFR2 (NCBI Reference Sequence NM 00109924.1; SEQ ID NO:25 peptide, SEQ ID NO:26 nucleotide), *Sus scrofa* FGFR3 (GenBank Accession No. BV726808.1; SEQ ID NO:27 cds nucleotide), *Sus scrofa* FGFR4 (NCBI Reference Sequence XM_003123682.1; SEQ ID NO:28 peptide, SEQ ID NO:29 nucleotide), *Macaca mulatta* FGF2 (NCBI Reference Sequence XM_001099284.2; SEQ ID NO:30 peptide, SEQ ID NO:31 nucleotide), *Macaca fascicularis* FGFR1 (GenBank Accession No. AB220417.1; SEQ ID NO:32 peptide, SEQ ID NO:33 nucleotide), *Macaca mulatta* FGFR2 partial (GenBank Accession No. AY083548.1; SEQ ID NO:34 peptide,

19

SEQ ID NO:35 nucleotide), *Macaca mulatta* FGFR3 (NCBI Reference Sequence XM_002802167.1; SEQ ID NO:36 peptide, SEQ ID NO:37 nucleotide), *Macata mulatta* FGFR4 (NCBI Reference Sequence XM_001087243.2; SEQ ID NO:38 peptide, SEQ ID NO:39 nucleotide), *Mus musculus* FGF2 (NCBI Reference Sequence NM_008006.2; SEQ ID NO:40 peptide, SEQ ID NO:41 nucleotide), *Mus musculus* FGFR1 (NCBI Reference Sequence NM_010206.2; SEQ ID NO:42 peptide, SEQ ID NO:43 nucleotide), *Mus musculus* FGFR2 (NCBI Reference Sequence NM_010207.2; SEQ ID NO:44 peptide, SEQ ID NO:45 nucleotide), *Mus musculus* FGFR3 (NCBI Reference Sequence NM_008010.4; SEQ ID NO:46 peptide, SEQ ID NO:47 nucleotide), and *Mus musculus* FGFR4 (NCBI Reference Sequence NM_008011.2; SEQ ID NO:48 peptide, SEQ ID NO:49 nucleotide).

Without limitation, the invention also provides methods for increasing endogenous antibody production in mammals such as humans by administering any of the following enumerated compounds or pharmacologically acceptable salts thereof:

1. BIBF1120 (Vargatef) Boehringer Ingelheim, chemical name: Methyl (3Z)-3-[{4-[N-methyl-2-(4-methylpiperazin-1-yl)acetamido]phenyl}amino](phenyl)methylidene]-2-oxo-2,3-dihydro-1H-indole-6-carboxylate.



F. Hilberg et al Cancer Res. 2008 Jun. 15; 68(12):4774-82. doi: 10.1158/0008-5472.CAN-07-6307. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy.

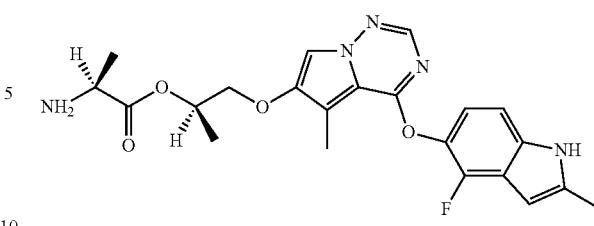
2. TKI258 (Dovitinib) Novartis, chemical name: 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzo[d]imidazol-2-yl]-3,4-dihydronaphthalen-2 (1H)-one



Trudel S, et al Blood. 2005 Apr. 1; 105(7):2941-8. Epub 2004 Dec. 14. CHIR-258, a novel, multitargeted tyrosine kinase inhibitor for the potential treatment of t(4;14) multiple myeloma.

3. BMS582664 (Brivanib) Bristol Myers Squib, chemical name: (1R)-2-[[4-[(4-fluoro-2-methyl-1H-indol-5-yl)oxy]-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]oxy]-1-methylethyl(2S)-2-aminopropanoate

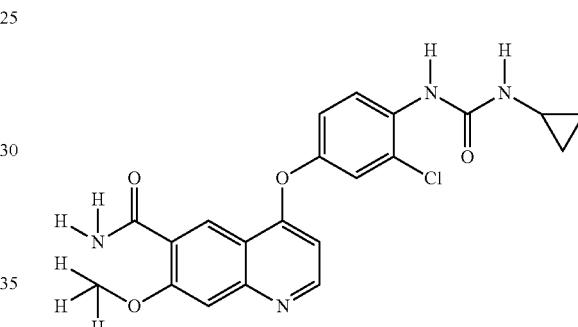
20



Bhide R S et al J Med. Chem. 2006 Apr. 6; 49(7):2143-6. Discovery and preclinical studies of (R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan-2-ol (BMS-540215), an in vivo active potent VEGFR-2 inhibitor.

20 4. E7080 Eisai

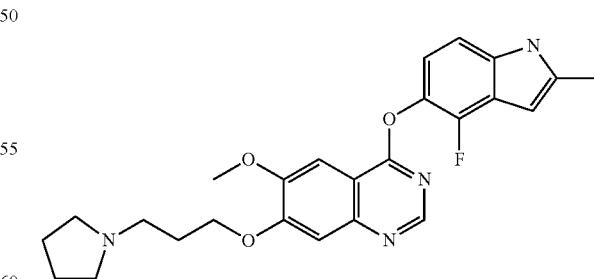
chemical name: 4-[3-Chloro-4-(3-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide



Boss D S et al Br J. Cancer. 2012 May 8; 106(10):1598-604. doi: 10.1038/bjc.2012.154. Epub 2012 Apr. 19. A phase I study of E7080, a multitargeted tyrosine kinase inhibitor, in patients with advanced solid tumours.

45 5. AZ2171 (Cediranib) Astra Zeneca

chemical name: 4-[(4-Fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline

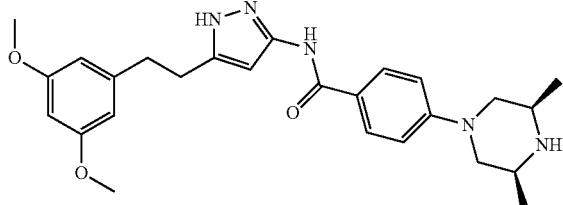


Wedge S R et al Cancer Res. 2005 May 15; 65(10):4389-400. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer.

21

6. AZD4547 Astra Zeneca

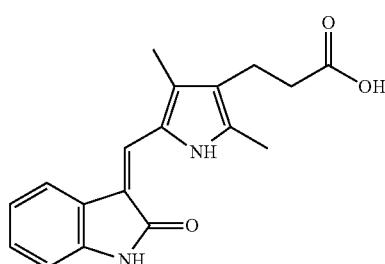
chemical name: N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,5-dimethylpiperazin-1-yl)benzamide



Gavine P R Cancer Res. 2012 Apr. 15; 72(8):2045-56. doi: 10.1158/0008-5472.CAN-11-3034. Epub 2012 Feb. 27. AZD4547: an orally bioavailable, potent, and selective inhibitor of the fibroblast growth factor receptor tyrosine kinase family.

7. TSU68(SU6668) Taiho Pharmaceutical

chemical name: (E)-3-[2,4-Dimethyl-5-[(2-oxoindolin-3-ylidene)methyl]-1H-pyrrol-3-yl]propanoic acid

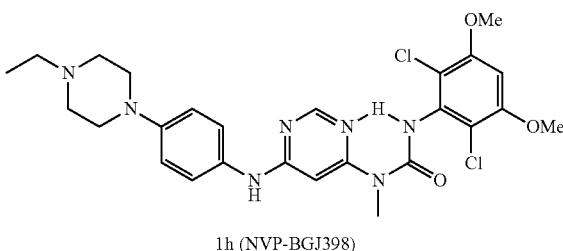


SU 6668

Yorozuya K, et al Oncol Rep. 2005 September; 14(3):677-82. TSU-68 (SU6668) inhibits local tumor growth and liver metastasis of human colon cancer xenografts via anti-angiogenesis.

8. BGJ398 Novartis

chemical name: 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea



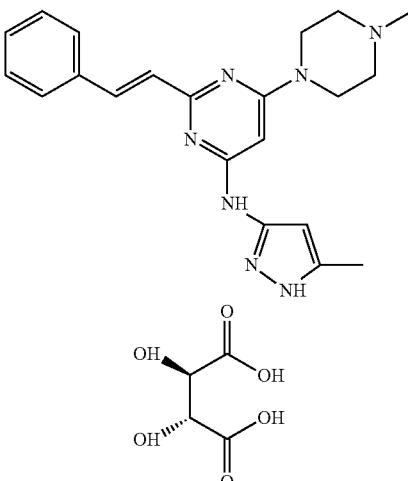
1h (NVP-BGJ398)

Guagnano V, et al J Med. Chem. 2011 Oct. 27; 54(20): 7066-83. doi: 10.1021/jm2006222. Epub 2011 Sep. 21. Discovery of 3-(2,6-dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea (NVP-BGJ398), a potent and selective inhibitor of the fibroblast growth factor receptor family of receptor tyrosine kinase.

22

9. ENMD2076 Miikana Therapeutics

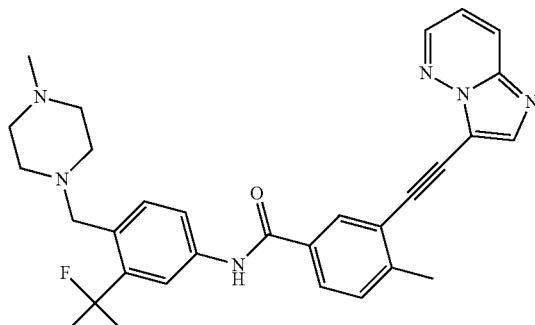
chemical name: 6-(4-Methylpiperazin-1-yl)-N-(5-methyl-1H-pyrazol-3-yl)-2-[(E)-2-phenylvinyl]pyrimidin-4-amine L-tartrate



Matulonis UA, et al Eur J. Cancer. 2013 January; 49(1):121-31. doi: 10.1016/j.ejca.2012.07.020. Epub 2012 Aug. 21. ENMD-2076, an oral inhibitor of angiogenic and proliferation kinases, has activity in recurrent, platinum resistant ovarian cancer.

10. AP24534 (Ponatinib) Ariad Pharmaceuticals

chemical name: Benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]



Chase A, et al. Haematologica. 2013 January; 98(1):103-6. doi: 10.3324/haematol.2012.066407. Epub 2012 Aug. 8. Ponatinib as targeted therapy for FGFR1 fusions associated with the 8p11 myeloproliferative syndrome.

11. AXL1717 Axlar

chemical name: Furo(3',4';6,7)naphtho(2,3-d)-1,3-dioxol-6(5aH)-one, 5,8,8a,9-tetrahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)-, (5R-(5-alpha,5a-alpha,8a-alpha,9-alpha))-

Ekman S, Acta Oncol. 2011 April; 50(3):441-7. doi: 10.3109/0284186X.2010.499370. Epub 2010 Aug. 11. Clinical Phase I study with an Insulin-like Growth Factor-1 receptor inhibitor: experiences in patients with squamous non-small cell lung carcinoma.

12. FP1039 (fusion protein) Five Prime, Human Genome Sciences, Glaxo Smith Kline. FP 1039 comprises the extra-

23

cellular domain of human fibroblast growth factor receptor 1c (FGFR1) linked to the Fc portion of human IgG1. The molecule is designed to trap FGFR1 ligands and prevent binding to FGF receptors. Harding et al., Preclinical efficacy of FP-1039 (FGFR1:Fc) in endometrial carcinoma models with activating mutations in FGFR2. 101st Annual Meeting of the American Association for Cancer Research.: abstr. 2597, 17 Apr. 2010

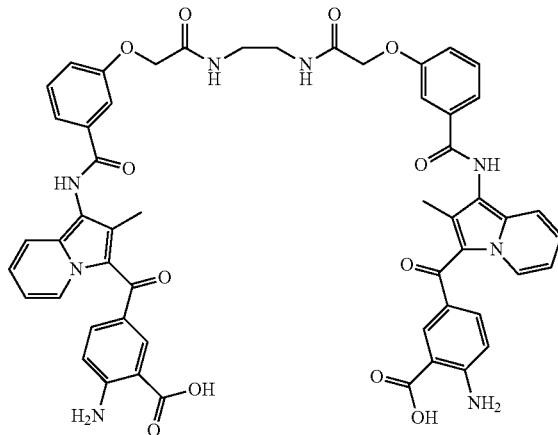
13. MGFR 1877S FGFR3Mab Genentech. Qing J et al J Clin Invest. 2009 May; 119(5):1216-29. doi: 10.1172/JCI38017. Epub 2009 Apr. 20. Antibody-based targeting of FGFR3 in bladder carcinoma and t(4;14)-positive multiple myeloma in mice.

14. Aveo GP369 FGFR2 mAb. Bai A Cancer Res. 2010 Oct. 1; 70(19):7630-9. doi: 10.1158/0008-5472.CAN-10-1489. Epub 2010 Aug. 13. GP369, an FGFR2-IIIb-specific antibody, exhibits potent antitumor activity against human cancers driven by activated FGFR2 signaling.

15. FGFR1 and FGFR3 mAbs Imclone Systems. Sun H D et al Am J Physiol Endocrinol Metab. 2007 March; 292(3): E964-76. Epub 2006 Nov. 28. Monoclonal antibody antagonists of hypothalamic FGFR1 cause potent but reversible hypophagia and weight loss in rodents and monkeys; Deevi D S, Direnzo R, Li H, Malabunga M, Prewett M C Inhibiting FGFR3 for enhancing the cytotoxic effects of cisplatin on bladder cancer cells and possible mechanisms. 2007 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.: 176-177 (plus poster) abstr. B48, 22 Oct. 2007.

16. FGF2 and FGFR2 mAbs Galaxy Biotech. Wang L, et al. Mol Cancer Ther. 2012 April; 11(4):864-72. doi: 10.1158/1535-7163.MCT-11-0813. Epub 2012 Feb. 16. A novel monoclonal antibody to fibroblast growth factor 2 effectively inhibits growth of hepatocellular carcinoma xenografts; Zhao W M, Clin Cancer Res. 2010 Dec. 1; 16(23):5750-8. doi: 10.1158/1078-0432.CCR-10-0531. Epub 2010 Jul. 29. Monoclonal antibodies to fibroblast growth factor receptor 2 effectively inhibit growth of gastric tumor xenografts.

17. SAR 106881, Sanofi Aventis Research program FGFR agonists



A name could not be generated for this structure

Guillo, Making agonists from antagonists: SAR106881, a breakthrough in FGFRs activation and a potential treatment to improve peripheral revascularization and reduce neuropathic pain. 240th National Meeting of the American Chemical Society.: (plus oral presentation) abstr. MEDI 23, 22 Aug. 2010.

24

18. JNJ 42756493 FGFR antagonists Astex Therapeutics/ Janssen Research. Squires et al., Development of inhibitors of the fibroblast growth factor receptor (FGFR) kinase using a fragment based approach. 101st Annual Meeting of the American Association for Cancer Research.: abstr. 3626, 17 Apr. 2010.

The compounds or pharmacologically acceptable salts thereof may, for example, be administered in therapeutically effective amounts to a mammal such as a human in need of increasing endogenous antibody production who is not in need of treatment for a cancer. The mammal may have an immune deficiency such as a humoral immune deficiency or any of the immune deficiencies described herein. The mammal may, for example, be geriatric. The compounds or pharmaceutically acceptable salts thereof, may for example, be administered in an amount effective to increase endogenous antibody production in conjunction with a vaccination with an immunogen (other than FGF2 or an FGF) to improve the humoral immune response to the vaccination. The compounds or pharmaceutically acceptable salts thereof, may for example, be administered in an amount effective to increase endogenous antibody production to a mammal, such as a human, in need of treatment for a microbial infection or viral infection, for example, alone or in addition to (or in conjunction with) administration of an antibiotic or antiviral agent. In any of the methods, the mammal may be one that is not in need of treatment for cancer. The invention also provides corresponding first and second medical uses for each of the methods of treatment described in this disclosure. Accordingly, the invention provides the use of the agents for modulating humoral immunity and for treatment of the conditions described and also provides use of the agents for the manufacture of medicaments for modulating humoral immunity and for the treatment of the conditions described herein.

Non-human mammals with which the invention may be used include, for example, livestock animals, such as Bovidae, for example cows and sheep, and swine, also Equidae such as horses, canines such as companion domesticated dogs and felines such as companion domesticated cats, primates, Lagomorphs such as rabbits and Rodentia such as rats and mice. The invention is also applicable in birds such as foul, for example, chickens, turkeys and quail, ducks and geese. Accordingly, the invention provides corresponding embodiments and variations as described herein for mammals but applied to avians, such as the aforementioned avians. The sequences of *Gallus gallus* FGF2 (NCBI Reference Sequence: NM_205433.1; SEQ ID NO:50 peptide, SEQ ID NO:51 nucleotide), *Gallus gallus* FGFR1 (NCBI Reference Sequence: NM_205510.1; SEQ ID NO:52 peptide, SEQ ID NO:53 nucleotide), *Gallus gallus* FGFR2 (NCBI Reference Sequence: NM_205319.1; SEQ ID NO:54 peptide, SEQ ID NO:55 nucleotide), and *Gallus gallus* FGFR3 (NCBI Reference Sequence: NM_205509.2; SEQ ID NO:56 peptide, SEQ ID NO:57 nucleotide) also form part of this disclosure.

While the above examples relate to FGF2 and its receptors, the invention also provides corresponding embodiments for each embodiment and variation described herein for a fibroblast growth factor and/or FGF receptor generally, and for other specific fibroblast growth factors such as, but not limited to, FGF1 and FGF3.

Each of the patents and other publications cited in this disclosure is incorporated by reference in its entirety.

Although the foregoing description is directed to the preferred embodiments of the invention, it is noted that other variations and modifications will be apparent to those skilled in the art, and may be made without departing from the spirit or scope of the invention. Moreover, features described in connection with one embodiment of the invention may be used in conjunction with other embodiments, even if not explicitly stated above.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 57

<210> SEQ ID NO 1

<211> LENGTH: 288

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

Met	Val	Gly	Val	Gly	Gly	Asp	Val	Glu	Asp	Val	Thr	Pro	Arg	Pro
1				5			10				15			

Gly	Gly	Cys	Gln	Ile	Ser	Gly	Arg	Gly	Ala	Arg	Gly	Cys	Asn	Gly	Ile
				20			25				30				

Pro	Gly	Ala	Ala	Ala	Trp	Glu	Ala	Ala	Leu	Pro	Arg	Arg	Arg	Pro	Arg
					35			40			45				

Arg	His	Pro	Ser	Val	Asn	Pro	Arg	Ser	Arg	Ala	Ala	Gly	Ser	Pro	Arg
					50			55			60				

Thr	Arg	Gly	Arg	Arg	Thr	Glu	Glu	Arg	Pro	Ser	Gly	Ser	Arg	Leu	Gly
					65			70			75				80

Asp	Arg	Gly	Arg	Arg	Gly	Ala	Leu	Pro	Gly	Gly	Arg	Leu	Gly	Arg
					85			90			95			

Gly	Arg	Gly	Arg	Ala	Pro	Glu	Arg	Val	Gly	Gly	Arg	Gly	Arg	
					100			105			110			

Gly	Thr	Ala	Ala	Pro	Arg	Ala	Ala	Pro	Ala	Ala	Arg	Gly	Ser	Arg	Pro
					115			120			125				

Gly	Pro	Ala	Gly	Thr	Met	Ala	Ala	Gly	Ser	Ile	Thr	Thr	Leu	Pro	Ala
					130			135			140				

Leu	Pro	Glu	Asp	Gly	Gly	Ser	Gly	Ala	Phe	Pro	Pro	Gly	His	Phe	Lys
						145		150			155				160

Asp	Pro	Lys	Arg	Leu	Tyr	Cys	Lys	Asn	Gly	Gly	Phe	Phe	Leu	Arg	Ile
					165			170			175				

His	Pro	Asp	Gly	Arg	Val	Asp	Gly	Val	Arg	Glu	Lys	Ser	Asp	Pro	His
					180			185			190				

Ile	Lys	Leu	Gln	Leu	Gln	Ala	Glu	Glu	Arg	Gly	Val	Val	Ser	Ile	Lys
					195			200			205				

Gly	Val	Cys	Ala	Asn	Arg	Tyr	Leu	Ala	Met	Lys	Glu	Asp	Gly	Arg	Leu
					210			215			220				

Leu	Ala	Ser	Lys	Cys	Val	Thr	Asp	Glu	Cys	Phe	Phe	Phe	Glu	Arg	Leu
					225			230			235				240

Glu	Ser	Asn	Asn	Tyr	Asn	Thr	Tyr	Arg	Ser	Arg	Lys	Tyr	Thr	Ser	Trp
					245			250			255				

Tyr	Val	Ala	Leu	Lys	Arg	Thr	Gly	Gln	Tyr	Lys	Leu	Gly	Ser	Lys	Thr
					260			265			270				

Gly	Pro	Gly	Gln	Lys	Ala	Ile	Leu	Phe	Leu	Pro	Met	Ser	Ala	Lys	Ser
					275			280			285				

<210> SEQ ID NO 2

<211> LENGTH: 6774

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

cggccccaga aaacccgagc gagtaggggg cggcgccgac gagggaggag aactgggggc 60

gcggggaggct ggtgggtgtg ggggggtggag atgtagaaga tgtgacgcgcg cggcccgccg 120

-continued

ggtgccagat tagcggacgc ggtgcccggc gttgcaacgg gatccggggc gctgcagctt	180
gggaggcggc tctccccagg cggcgccgc ggagacaccc atccgtgaac cccaggtccc	240
ggggccgcgg ctcgecgccgc accaggggcg ggcggacaga agagcggccg agcggctcga	300
ggctggggga ccgcggggcgc ggccggcgc tgccggggc gaggctgggg ggccggggcc	360
ggggccgtgc cccggagcgg gtcggaggcc gggggccgggg cggggggacg gcggtcccc	420
gcgcggctcc agcggctcg ggtatccggc cggggccccc agggaccatg gcagecggga	480
gcatcaccac gctgeccgcc ttgcccgagg atggcggcag cggcgecttc cggccggcc	540
acttcaagga ccccaagcgg ctgtactgca aaaacggggg cttcttcctg cgcatccacc	600
ccgacggccg agttgacggg gtccgggaga agagcggaccc tcacatcaag ctacaacttc	660
aagcagaaga gagaggagtt gtgtctatca aaggagtgtg tgctaaccgt tacctggcta	720
tgaaggaaga tggaaagatta ctggcttcta aatgtttac ggtatgagtgt ttctttttg	780
aacgatttga atctaataac tacaataactt accggtaaag gaaatacacc agttggatg	840
tggcactgaa acgaactggg cagtataaac ttggatccaa aacaggaccc gggcagaaaag	900
ctatactttt tcttccaaatg tctgctaaga gctgatttta atggccacat ctaatctcat	960
ttcacatgaa agaagaagta tatttttagaa atttgttaat gagagtaaaa gaaaataaat	1020
gtgtatagct cagtttggat aatttgtcaa acaatttttt atccagtagt aaaatatgtta	1080
accatttgtcc cagtaaagaa aaataacaaa agttgtaaaaa tgtatattct ccctttata	1140
ttgcacatgtc tgtaacccag tgaagcttac cttagagcaat gatcttttc acgcatttgc	1200
tttattcgaa aagaggcttt taaaatgtc atgttttagaa acaaatttc ttcatggaaa	1260
tcatatacat tagaaaatca cagtcagatg tttaatcaat ccaaaatgtc cactattct	1320
tatgtcattc gtttagtctac atgtttctaa acatataaat gtgaatttaa tcaattcctt	1380
tcatagttt ataattctct ggcagttct tatgatagag tttataaaac agtccctgtgt	1440
aaactgctgg aagttttcc acagtccaggta caattttgtc aaacccttct ctgtaccat	1500
acagcagcag octagcaact ctgctggta tgggagttgt atttcagtc ttgcggaggt	1560
cattgagatc catccactca catcttaaagc attcttcctg gaaaaaattt atggtaatg	1620
aatatggctt tagggggcag atgatataca tatctgactt cccaaaagct ccaggattt	1680
tgtgctgttg ccgaaatactc aggacggacc tgaatttgc ttttataccca gtctttcaa	1740
aaacttctcg aaccgctgtg tcttctacgt aaaaaaagag atgtacaat caataataat	1800
tacactttta gaaactgtat catcaaagat ttctcgtttaa agtagcatat tggatggct	1860
caaaacatta ccctaacaaa gtaaaatttt caatacaaat tctttgcctt gtggatata	1920
agaaatccca aaatattttc ttaccactgt aaattcaaga agctttgaa atgctgaaata	1980
tttcttggc tgctacttgg aggcttatct acctgtacat ttttggggc agctttttt	2040
aacttctgc tgctttttt cccaaaaggat aaaaatatacg attgaaaatgt taaaacattt	2100
tgcatggctg cagttccctt gtttcttgcgataagattcc aaagaactta gattcattc	2160
ttcaacaccc aatgctggc ggtgtttgtat cagtttcaaa gaaacttggaa atataaataa	2220
ttttataattt caacaaaggat ttccacattt tataagggtt attttcaat taaatgcaaa	2280
tttgtgtggc aggatttta ttgccattaa catattttg tggctgtttt ttctacacat	2340
ccagatggc octctaaactg ggctttctct aattttgtga tggctgtca ttgtctccca	2400
aagtatttag gagaagccct taaaaaagct gccttcctct accacttgc tggaaagctt	2460
cacaattgtc acagacaaag attttgttc caataactcgt ttgcctcta ttttctgt	2520

-continued

ttgtcaaata gtaaaatgata tttgcccttg cagtaattct actggtgaaa aacatgcaaa	2580
gaagagagaag tcacagaaaac atgtctcaat tcccatgtgc tgtgactgta gactgtctta	2640
ccatagactg tcttacccat cccctggata tgctcttgg tttccctct aatacgat	2700
gaaagatgca tagaaaagagt ataatgtttt aaaacataag gcattcgctc gccattttc	2760
aattacatgc tgactccct tacaatttag atttgcccatt aggttaaaca tggtagaaa	2820
caactgaaag cataaaagaa aaatcttaggc cgggtgcagt ggctcatgcc tatattccct	2880
gcactttggg aggccaaagc aggaggatcg cttagccccca ggagttcaag accaacctgg	2940
tgaaaccccg tctctacaaa aaaacacaaa aaatagccg gcatggtggc gtgtacatgt	3000
ggtctcagat acttgggagg ctgaggtggg agggttgatc acttgaggct gagaggtcaa	3060
ggttgcagtgc agccataatc gtgcactgc agtccagecct aggcaacaga gtgagacttt	3120
gtctcaaaaa aagagaaaatt ttccttaata agaaaagtaa ttttactct gatgtcaat	3180
acattttgttata tatttaagat ggtagcacta gtcttaattt gtataaaata	3240
tcccttaaca tgtttaatg tccatttttta ttcatatgc tttgaaaaat aattatgggg	3300
aaatacatgt ttgttattaa atttattaa aaagatagta gcaactatct taaatttgat	3360
ataacatctc ctaacttgg taaatgtcca ttttattct ttatgtttga aaataaaatta	3420
tggggatcct attagctct tagtaccact aatcaaaagt tggcatgtc gctcatgtc	3480
tatgctgttt ctatgtcggt gaagcacccgg atgggggttag tgagcaatc tgccctgctc	3540
agcagtcacc atageagctg actgaaaatc agcactgcct gaggatgtt gatcgttta	3600
acttgaatca ctaactgact gaaaattgaa tggcaaaata agtgcttttgc tctccagat	3660
atgcgggaga ccctccacc tcaagatgga tattttctcc ccaaggattt caagatgaaat	3720
tgaaattttt aatcaagata gtgtgttta ttctgttgg ttttttattt ttttaatata	3780
ctgtaaagcca aactgaaata acattgtcg ttttataagggt ttttataatc taggaaaaac	3840
taagaggat ttgttttattt ttgtgtatc aagagatatg ttttataatc ttgttattgtt	3900
ttgttttagt acaggacaat aatgaaatgg agtttatatt ttgttatttct attttgttat	3960
atttataat agaatttagat tggaaataaaa tataatggg aataatctgc agaatgtggg	4020
ttttccctggt gttccctct gactctatgc cactgatgtat ctctgataag gctcagctgc	4080
tttatagttc tctggctaat gcagcagata ctcttctgc cagtgtaat acgattttt	4140
aagaaggcag ttgtcaatt ttaatcttgc ggataccctt atactcttag ggtattttt	4200
tatacaaaaag ccttgaggat tgcattctat tttctatatg acccttttgc tattttttttt	4260
acactatgga taacaattct tcatttacat agtattatgc aagaatgaaat gagttcaac	4320
aaatgtgtttt cccagtttac tagggtttac ttgttgcgc aatataatg tttaactgtt	4380
tgtgtatggc gtattccctaa agtacattgc atgttttccctt aaatacagat ttttataat	4440
ttcagtaattt ctttagatgtat tcagttcat cattaagaat atcttttgc ttatgttgc	4500
tttagaaatgc cttcatatag acatagtctt tcagacccctt actgtcaggat ttcatatct	4560
gtgtgtttca ggggtttatg aattttcagg caaagcttta atttataacta agcttaggaa	4620
gtatggctaa tgccaaacggc agtttttttc ttcttaatttcc cacatgactg aggcatatat	4680
gatctctggg taggtgagtt ttgtgtacaa ccacaaggac tttttttttt ttttaagaaaa	4740
aaaaggatgtt gatattttaa tcatctggac tttaagaagg attctggatc atacttaggc	4800
ctgaaattat atatattttgg cttggaaatg tgttttctt caattacatc tacaagtaag	4860

-continued

tacagctgaa attcagagga cccataagag ttcacatgaa aaaaatcaat ttatttggaa	4920
aggcaagatg caggagagag gaagccttgc aaacctgcag actgcgtttt gcccaatata	4980
gattgggtaa ggctgcaaaa cataagctta attagctcac atgctctgct ctcaegtggc	5040
accagtggat agtgtgagag aattaggctg tagaacaat ggccttctct ttcagcatc	5100
acaccactac aaaatcatct ttatatacaa cagaagaata agcataaact aagcaaagg	5160
tcaataagta cctgaaacca agattggcta gagatataatc ttaatgcaat ccatttctg	5220
atggattgtt acgagttggc tatataatgt atgtatggta ttttgatttg tgtaaaagtt	5280
ttaaaaatca acgtttaagt acatggacat tttaataataa aatatttaaa gacaatttag	5340
aaaattgcct taatatcatt gttggctaaa tagaataggg gacatgcata ttaaggaaaa	5400
ggtcatggag aaataataattt ggtatcaaac aaatacattt atttgcattg atacacattt	5460
aatttgcattt aatagttaa ggaataggta ggaaaatttg gtttctattt ttgcatttcc	5520
tgtaaatcag tgacataat aattcttagc ttatTTATAA tttccttgc ttAAataactg	5580
agctcagtaa gttgtgttag gggatttattt ctcagttgag acttttttat atgacatttt	5640
actatgtttt gacttcctga ctatTTAAA taaatagtag atacaatttt cataaagtga	5700
agaattataat aatcactgct ttataactga ctttattata ttatTTCAA agttcattha	5760
aaggctacta ttcatcctct gtgtatggaaat ggtcaggaat ttgtttctc atagttat	5820
tccaacaaca atattagtcg tatccaaaat aacctttaat gctaaacttt actgtatgtat	5880
atccaaagct tctcatTTTC agacagatta atccagaagc agtcataaac agaagaatag	5940
gtggatgtttt cctaatgata ttatTTCTAC taatggataa aactgtataa tttagaaat	6000
tgcgtctaat tatatcagct ctgaggtaat ttctgaaatg ttcaagactca gtcggacaa	6060
attggaaat taaaattttt attcttagct ataaagcaag aaagtaaaaca cattaattt	6120
ctcaacatTTT ttaagccaat taaaatataa aaagatacac accaataatct tcTTcaggct	6180
ctgacaggccc tcctggaaac ttccacatat ttTCAACTG cagttaaaag tcagaaaata	6240
aagttaacat aacttcact aacacacaca tatgttagatt tcacaaaatc cacctataat	6300
tggtaaagt ggttggaaat atatTTTTA gtaatttgcattt gcaaaaatttt tctagttcc	6360
atccTTTCTC ctcgtttct tcttttttg ggggagctgg taactgtatga aatTTTTCC	6420
cacctttctt ctTCAGGAAA tataagtgggt tttgtttggtaaactgtataa cattctgtat	6480
gaatgaaaca ttggaggggaa acatctactg aatttctgtat attaaaata ttTGTGCT	6540
agtttaactat gaacagatag aagaatctta cagatgtgc tataaaataag tagaaaat	6600
aaatttcatc actaaaatata gctatTTAA aatctatttcc ctatattgtat ttTCTAATCA	6660
gatgttattac tcttattatt tctattgtat gtgttaatgtat ttTGTGCTAA aatgtat	6720
gttttcatg agtagtatgata ataaaattgtat ttagtttgc ttTCTTGC tccc	6774

<210> SEQ ID NO 3

<211> LENGTH: 733

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Met	Trp	Ser	Trp	Lys	Cys	Leu	Leu	Phe	Trp	Ala	Val	Leu	Val	Thr	Ala
1				5			10			15					

Thr	Leu	Cys	Thr	Ala	Arg	Pro	Ser	Pro	Thr	Leu	Pro	Glu	Gln	Asp	Ala
20				25					30						

Leu Pro Ser Ser Glu Asp Asp Asp Asp Asp Asp Ser Ser Ser Glu

-continued

35	40	45
Glu Lys Glu Thr Asp Asn Thr Lys Pro Asn Arg Met Pro Val Ala Pro		
50	55	60
Tyr Trp Thr Ser Pro Glu Lys Met Glu Lys Lys Leu His Ala Val Pro		
65	70	75
80		
Ala Ala Lys Thr Val Lys Phe Lys Cys Pro Ser Ser Gly Thr Pro Asn		
85	90	95
Pro Thr Leu Arg Trp Leu Lys Asn Gly Lys Glu Phe Lys Pro Asp His		
100	105	110
Arg Ile Gly Gly Tyr Lys Val Arg Tyr Ala Thr Trp Ser Ile Ile Met		
115	120	125
Asp Ser Val Val Pro Ser Asp Lys Gly Asn Tyr Thr Cys Ile Val Glu		
130	135	140
Asn Glu Tyr Gly Ser Ile Asn His Thr Tyr Gln Leu Asp Val Val Glu		
145	150	155
160		
Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Lys		
165	170	175
Thr Val Ala Leu Gly Ser Asn Val Glu Phe Met Cys Lys Val Tyr Ser		
180	185	190
Asp Pro Gln Pro His Ile Gln Trp Leu Lys His Ile Glu Val Asn Gly		
195	200	205
Ser Lys Ile Gly Pro Asp Asn Leu Pro Tyr Val Gln Ile Leu Lys Thr		
210	215	220
Ala Gly Val Asn Thr Thr Asp Lys Glu Met Glu Val Leu His Leu Arg		
225	230	235
240		
Asn Val Ser Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn		
245	250	255
Ser Ile Gly Leu Ser His His Ser Ala Trp Leu Thr Val Leu Glu Ala		
260	265	270
Leu Glu Glu Arg Pro Ala Val Met Thr Ser Pro Leu Tyr Leu Glu Ile		
275	280	285
Ile Ile Tyr Cys Thr Gly Ala Phe Leu Ile Ser Cys Met Val Gly Ser		
290	295	300
Val Ile Val Tyr Lys Met Lys Ser Gly Thr Lys Lys Ser Asp Phe His		
305	310	315
320		
Ser Gln Met Ala Val His Lys Leu Ala Lys Ser Ile Pro Leu Arg Arg		
325	330	335
Gln Val Thr Val Ser Ala Asp Ser Ser Ala Ser Met Asn Ser Gly Val		
340	345	350
Leu Leu Val Arg Pro Ser Arg Leu Ser Ser Ser Gly Thr Pro Met Leu		
355	360	365
Ala Gly Val Ser Glu Tyr Glu Leu Pro Glu Asp Pro Arg Trp Glu Leu		
370	375	380
Pro Arg Asp Arg Leu Val Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe		
385	390	395
400		
Gly Gln Val Val Leu Ala Glu Ala Ile Gly Leu Asp Lys Asp Lys Pro		
405	410	415
Asn Arg Val Thr Lys Val Ala Val Lys Met Leu Lys Ser Asp Ala Thr		
420	425	430
Glu Lys Asp Leu Ser Asp Leu Ile Ser Glu Met Glu Met Met Lys Met		
435	440	445
Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln		
450	455	460

-continued

Asp Gly Pro Leu Tyr Val Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu
 465 470 475 480
 Arg Glu Tyr Leu Gln Ala Arg Arg Pro Pro Gly Leu Glu Tyr Cys Tyr
 485 490 495
 Asn Pro Ser His Asn Pro Glu Glu Gln Leu Ser Ser Lys Asp Leu Val
 500 505 510
 Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala Ser Lys
 515 520 525
 Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu
 530 535 540
 Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Ile His
 545 550 555 560
 His Ile Asp Tyr Tyr Lys Thr Asn Gly Arg Leu Pro Val Lys
 565 570 575
 Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Ile Tyr Thr His Gln Ser
 580 585 590
 Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr Leu Gly
 595 600 605
 Gly Ser Pro Tyr Pro Gly Val Pro Val Glu Glu Leu Phe Lys Leu Leu
 610 615 620
 Lys Glu Gly His Arg Met Asp Lys Pro Ser Asn Cys Thr Asn Glu Leu
 625 630 635 640
 Tyr Met Met Arg Asp Cys Trp His Ala Val Pro Ser Gln Arg Pro
 645 650 655
 Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Ile Val Ala Leu Thr
 660 665 670
 Ser Asn Gln Glu Tyr Leu Asp Leu Ser Met Pro Leu Asp Gln Tyr Ser
 675 680 685
 Pro Ser Phe Pro Asp Thr Arg Ser Ser Thr Cys Ser Ser Gly Glu Asp
 690 695 700
 Ser Val Phe Ser His Glu Pro Leu Pro Glu Glu Pro Cys Leu Pro Arg
 705 710 715 720
 His Pro Ala Gln Leu Ala Asn Gly Gly Leu Lys Arg Arg
 725 730

<210> SEQ ID NO 4
 <211> LENGTH: 3365
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

```

gcaccgagcg ccggccggag tcgagcgccg gcccggggc tcttgcgacc ccggcaggac      60
ccgaacagag cccggggcg gcggggccga gcccggggacg cgggcacacg cccgctcgca    120
caagccacgg cggactctcc cgaggcggaa cttcacgcg gagcgggggt cagttgaaa     180
aggaggatcg agctcactgt ggagtatcca tggagatgtg gagccttgtc accaacctct   240
aactgcagaa ctggatgtg gagctgaa tgccctctct tctgggtgt gctggtcaca    300
gccacacact gcaccgctag gccgtccccg accttgctg aacaagatgc tctccctcc   360
tcggaggatg atgatgatga tcatgactcc tcttcagagg agaaagaaac agataacacc  420
aaaccaaacc gtatgcccgt agctccatat tggacatccc cagaaaagat ggaaaagaaa  480
ttgcatgcag tgccggctgc caagacagtg aagttcaaat gcccttccag tgggacccca  540
aaccccacac tgcgctggtt gaaaaatggc aaagaattca aacctgacca cagaattgga  600

```

-continued

ggctacaagg tccgttatgc cacctggagc atcataatgg actctgtggt gccccttgac	660
aaggggcaact acacacctgcat tgtggagaat gagtacggca gcatcaacca cacataccag	720
ctggatgtcg tggagcggtc ccctcaccgg cccatcctgc aagcagggtt gcccggcaac	780
aaaacagtgg ccctgggttag caacgtggag ttcatgtgta aggtgtacag tgacccgcag	840
ccgcacatcc agtggctaaa gcacatcgag gtgaatggga gcaagattgg cccagacaac	900
ctgccttatg tccagatctt gaagactgct ggagttataa ccacccgacaa agagatggag	960
gtgcttcaact taagaatgt ctccctttag gacgcagggg agtatacgtg cttggcggtt	1020
aactctatcg gactctccca tcactctgca tgggtgaccg ttctggaaagc cctggaaagag	1080
aggccggcag tcatgaccc tcacccgtac ctggagatca tcatctattg cacaggggcc	1140
ttcctcatct octgcatggt ggggtcggtc atcgtctaca agatgaagag tggtaccaag	1200
aagagtgact tccacagcca gatggctgtg cacaagctgg ccaagagcat ccctctgcgc	1260
agacaggtaa cagtgtctgc tgactccagt gcatccatga actctgggtt tcttctggtt	1320
cggccatcac ggctctccctc cagtggtggact cccatgttag caggggtctc tgagtatgag	1380
cttccccaaag accctcgctg ggagctgcct cgggacagac tgggtcttagg caaacccctg	1440
ggagagggct gcttggca ggttgtgttg gcagaggota tgggtctgga caaggacaaa	1500
cccaaccctg tgaccaaagt ggctgtgaag atggtgaagt cggacgcac agagaaagac	1560
ttgtcagacc tcatctcaga aatggagatg atgaagatga tgggaagca taagaatatc	1620
atcaaccatgc tggggccctg cacgcaggat ggtcccttg atgtcatcgt ggagtatgcc	1680
tccaaggggca acctgccccg gtacctgcag gcccggaggc ccccaagggtt ggaatactgc	1740
tacaacccca gccacaaccc agaggagcag ctctccctca aggacctggt gtcctgcgcc	1800
taccaggtgg cccgaggcat ggagtatctg gcctccaaga agtgcataca ccgagacactg	1860
gcagccagga atgtcttggt gacagaggac aatgtgtatc agatagcaga ctttggctc	1920
gcacgggaca ttcaccacat cgactactat aaaaagacaa ccaacggcccg actgctgtg	1980
aagtggatgg cacccggaggc attatttgc cggatctaca cccaccagag tggatgtgtgg	2040
tcttccgggg tgctctgtg ggagatcttc actctggcg gctcccccata ccccggtgtg	2100
cctgtggagg aactttcaa gctgctgaag gagggtcacc gcatggacaa gcccagtaac	2160
tgcaccaacg agctgtacat gatgtgtgg gactgctggc atgcagtgcc ctcacagaga	2220
cccacccatca agcagctggt ggaagacactg gaccgcattg tggccttgac ctccaaaccag	2280
gagttacctgg acctgtccat gcccctggac cagttactccc ccagctttcc cgacacccgg	2340
agctctacgt gtcctcagg ggaggattcc gtcttctctc atgagccgt gcccggaggag	2400
cctgtccctgc cccgacaccc agcccagttt gccaatggcg gactcaacacg ccgtactg	2460
ccacccacac gcccctccca gactccacccg tcagctgtaa ccctcaccac cagccccctgc	2520
tggggccacc acctgtccgt ccctgtcccc tttcctgtg tggaggagccg gctgcctacc	2580
agggggcttc ctgtgtggcc tgccttcacc ccactcagct cacctctccc tccacccct	2640
ctccacatgc tggatgtggagg tggcaaaagag gcatgtttt gtcggccagcc acttcatccc	2700
ctcccaatgtg tggacccac accccctccct gccaccaggc actgctgtgg gggcaggag	2760
tggggccacc tgaacaggca tgcaagttgg agcttctgtg gttttctct gtcgggttgg	2820
tctgttttgc cttcacccat aagccccctcg cactctggtg gcaggtgcct tgcctcagg	2880
gtacacagcag tagggaggcag agtgcctcgat gctcgattg aaggtgaccc ctgccccaga	2940

-continued

taggtggtgc cagtggctta ttaattccga tactagtttg ctttgcacaaatgcctg	3000
gtaccagagg atggtgaggc gaaggccagg ttggggcag tggtgtggcc ctggggccca	3060
gccccaaact gggggctctg tatatagcta tgaagaaaac acaaagtgtaaatctgag	3120
tatataatcta catgtcttt taaaaggcgtt accatccat cgggtaaat	3180
gctcctggtg gctgggagc atcagttgtatataataaa aacaaaaaag aaaaaaaagg	3240
aaaacgtttt taaaaggcgtt atatatttt tgctactttt gctgttttat ttttttaat	3300
tatgttctaa acctatttc agtttaggtc cctcaataaa aattgtgtgtt gcttcaaaaa	3360
aaaaaa	3365

<210> SEQ ID NO 5
<211> LENGTH: 821
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Met Val Ser Trp Gly Arg Phe Ile Cys Leu Val Val Val Thr Met Ala	
1 5 10 15	
Thr Leu Ser Leu Ala Arg Pro Ser Phe Ser Leu Val Glu Asp Thr Thr	
20 25 30	
Leu Glu Pro Glu Glu Pro Pro Thr Lys Tyr Gln Ile Ser Gln Pro Glu	
35 40 45	
Val Tyr Val Ala Ala Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu	
50 55 60	
Lys Asp Ala Ala Val Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly	
65 70 75 80	
Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly	
85 90 95	
Ala Thr Pro Arg Asp Ser Gly Leu Tyr Ala Cys Thr Ala Ser Arg Thr	
100 105 110	
Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile	
115 120 125	
Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Gly Ala Glu Asp Phe Val	
130 135 140	
Ser Glu Asn Ser Asn Asn Lys Arg Ala Pro Tyr Trp Thr Asn Thr Glu	
145 150 155 160	
Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys	
165 170 175	
Phe Arg Cys Pro Ala Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu	
180 185 190	
Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys	
195 200 205	
Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser	
210 215 220	
Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile	
225 230 235 240	
Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro	
245 250 255	
Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly	
260 265 270	
Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile	
275 280 285	
Gln Trp Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp	

-continued

290	295	300
Gly Leu Pro Tyr Leu Lys Val Leu Lys Ala Ala Gly Val Asn Thr Thr		
305	310	315
Asp Lys Glu Ile Glu Val Leu Tyr Ile Arg Asn Val Thr Phe Glu Asp		
325	330	335
Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Ile Ser Phe		
340	345	350
His Ser Ala Trp Leu Thr Val Leu Pro Ala Pro Gly Arg Glu Lys Glu		
355	360	365
Ile Thr Ala Ser Pro Asp Tyr Leu Glu Ile Ala Ile Tyr Cys Ile Gly		
370	375	380
Val Phe Leu Ile Ala Cys Met Val Val Thr Val Ile Leu Cys Arg Met		
385	390	395
Lys Asn Thr Thr Lys Lys Pro Asp Phe Ser Ser Gln Pro Ala Val His		
405	410	415
Lys Leu Thr Lys Arg Ile Pro Leu Arg Arg Gln Val Thr Val Ser Ala		
420	425	430
Glu Ser Ser Ser Met Asn Ser Asn Thr Pro Leu Val Arg Ile Thr		
435	440	445
Thr Arg Leu Ser Ser Thr Ala Asp Thr Pro Met Leu Ala Gly Val Ser		
450	455	460
Glu Tyr Glu Leu Pro Glu Asp Pro Lys Trp Glu Phe Pro Arg Asp Lys		
465	470	475
Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val Val		
485	490	495
Met Ala Glu Ala Val Gly Ile Asp Lys Asp Lys Pro Lys Glu Ala Val		
500	505	510
Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Glu Lys Asp Leu		
515	520	525
Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys His		
530	535	540
Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu		
545	550	555
Tyr Val Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu		
565	570	575
Arg Ala Arg Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp Ile Asn Arg		
580	585	590
Val Pro Glu Glu Gln Met Thr Phe Lys Asp Leu Val Ser Cys Thr Tyr		
595	600	605
Gln Leu Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile His		
610	615	620
Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asn Asn Val Met		
625	630	635
Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Ile Asn Asn Ile Asp Tyr		
645	650	655
Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala Pro		
660	665	670
Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp Ser		
675	680	685
Phe Gly Val Leu Met Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr		
690	695	700
Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly His		
705	710	715
		720

-continued

Arg	Met	Asp	Lys	Pro	Ala	Asn	Cys	Thr	Asn	Glu	Leu	Tyr	Met	Met
725									730					735

Arg	Asp	Cys	Trp	His	Ala	Val	Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys	Gln
740							745							750	

Leu	Val	Glu	Asp	Leu	Asp	Arg	Ile	Leu	Thr	Leu	Thr	Thr	Asn	Glu	Glu
755							760						765		

Tyr	Leu	Asp	Leu	Ser	Gln	Pro	Leu	Glu	Gln	Tyr	Ser	Pro	Ser	Tyr	Pro
770							775						780		

Asp	Thr	Arg	Ser	Ser	Cys	Ser	Ser	Gly	Asp	Asp	Ser	Val	Phe	Ser	Pro
785					790			795						800	

Asp	Pro	Met	Pro	Tyr	Glu	Pro	Cys	Leu	Pro	Gln	Tyr	Pro	His	Ile	Asn
805							810						815		

Gly	Ser	Val	Lys	Thr											
				820											

<210> SEQ_ID NO 6

<211> LENGTH: 4654

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

ggcgccggct	ggaggagagc	gcccgtggaga	gcccggcg	ccccggcg	gtgcggagcg	60
ggcgaggggag	cgcgcgcggc	cgcacaaag	ctcggggcgc	cgggggctgc	atgcggcgta	120
cctggccccc	cgcggcgact	gctctccggg	ctggcggggg	ccggccgcga	gccccgggg	180
cccccgaggcc	gcagcttgcc	tgcgcgctct	gagccttcgc	aactcgcgag	caaagtgg	240
tggaggcaac	gccaaggctg	agtcccttct	tcctctcggt	ccccaaatcc	gagggcagcc	300
cgcggggcgtc	atgcggcg	tcctccgcag	cctgggttac	gcgtgaagcc	cggggaggctt	360
ggcgccggcg	aagacccaag	gaccacttt	ctgcgtttgg	agttgtcc	cgcaaccccg	420
ggctcgctgc	tttctccatc	ccgaccacag	cgggggcg	ggacaacaca	ggtcgcggag	480
gagcgttgcc	attcaagtga	ctgcagcagc	agcggcagcg	cctcggttcc	tgagcccacc	540
gcaggcgtaa	ggcattgcgc	gtatgccat	cccgtagagg	aagtgtcg	atgggattaa	600
cgtccacatg	gagatatgga	agaggaccgg	ggattggta	cgttaaccatg	gtcagctgg	660
gtcggttcat	ctgcctggc	gtggtcacca	tggcaacctt	gtccctggcc	cggccctcct	720
tcaagttagt	tgaggatacc	acattagagc	cagaagagcc	accaaccaa	taccaaatt	780
ctcaaccaga	agtgtacgt	gctgcgcac	ggggatgcgt	agaggtgc	tgcctgttga	840
aagatgcgc	cgtgtatcgt	tggactaagg	atggggtgca	cttggggccc	aacaatagga	900
cagtgttat	tggggatgt	ttgcagataa	agggcgccac	gcctagagac	tccggccct	960
atgcgttgc	tgcctgttgc	actgttagaca	gtgaaacttg	gtacttcat	gtaatgtca	1020
cagatgcac	tcatccgg	gatgtgagg	atgacaccga	tgggtggaa	gatttgtca	1080
gtgagaacag	taacaacaag	agagcacat	actggacca	cacagaaa	atggaaa	1140
ggctccatgc	tgtgcctgc	gccaacactg	tcaagttcg	ctgcccagcc	ggggggaa	1200
caatgcac	catgcgg	ctgaaaaacg	ggaagggtt	taagcaggag	catcgatt	1260
gaggctacaa	ggtacgaaac	cagcacttgg	gcctcattat	ggaaagtgt	gtcccatct	1320
acaaggaaaa	ttatacctgt	gtatggaga	atgaatacg	gtccatca	cacacgtacc	1380
acctggatgt	tgtggagcg	tcgcctcacc	ggcccatcct	ccaagccg	ctgcggca	1440
atgcctccac	agtggtcgg	ggagacgt	agttgtct	caaggtttac	agtgtatccc	1500

-continued

agccccacat ccagtggatc aagcacgtgg aaaagaacgg cagtaatac gggcccgacg	1560
ggctgcctca cctcaagggtt ctcaggccg ccgggtgttaa caccacggac aaagagattg	1620
aggttctcta tattcggaat gtaacttttg aggacgctgg ggaatatacg tgcttggcg	1680
gtaattctat tggatatacc ttctactctg catggttgac agttctgcc agcgcctggaa	1740
gagaaaagga gattacagct tccccagact acctggagat agccattac tgcatagggg	1800
tcttcataat cgccctgtatg gtggtaacag tcatcctgtg ccgaatgaag aacacgacca	1860
agaagccaga cttcagcage cagccggctg tgccacaagct gaccaaact atccccctgc	1920
ggagacaggt aacagttcg gctgagtc a gtcctccat gaactccaac accccgctgg	1980
tgaggataac aacacgcctc tcttcaacgg cagacacccc catgctggca ggggtctccg	2040
agtatgaact tccagaggac cccaaatggg agtttccaag agataagctg acactggca	2100
agccccctggg agaagggttgc tttggcaag tggcatggc ggaagcagtg ggaattgaca	2160
aagacaagcc caaggaggcg gtcaccgtgg ccgtgaagat gttgaaagat gatgccacag	2220
agaaagacct ttctgatctg gtgtcagaga tggagatgat gaagatgatt gggaaacaca	2280
agaatatcat aaatcttctt ggacccctca cacaggatgg gtcctctat gtcatagttg	2340
agtatgcctc taaaggcaac ctccgagaat acctccgagc ccggaggccca cccggatgg	2400
agtactctca tgacattaac cgtgttccctg aggaggcagat gacccctcaag gacttgggt	2460
catgcaccta ccacgtggcc agaggcatgg agtacttggc ttcccaaaaa tgtattcatc	2520
gagatttagc agccagaaat gttttggtaa cagaaaacaa tgtgatgaaa atagcagact	2580
ttggactcgc cagagatatac aacaatatac actattacaa aaagaccacc aatggccgc	2640
ttccagtcaa gtggatggct ccagaagccc tggatggatag agtataact catcagagt	2700
atgtctggtc ttccgggtg ttaatgtggg agatcttac tttagggggc tcgcctacc	2760
cagggattcc cgtggaggaa cttttaagc tgctgaagga aggacacaga atggataagc	2820
cagccaaactg caccaacgaa ctgtacatga tgatggggc ctgtggcat gcagtgcct	2880
cccgagacc aacgttcaag cagttggtag aagacttggc tgcattctc actctcacaa	2940
ccaatgagga atacttggac ctcagccaa ctctcgaaca gtattcacct agttaccctg	3000
acacaagaag ttcttgttct tcaggagatg attctgtttt ttctccagac cccatgcctt	3060
acgaaccatg cttectctag tatccacaca taaacggcag tgtaaaaca tgaatgactg	3120
tgtctgcctg tccccaaaca ggacagcact gggAACCTAG ctacactgag cagggagacc	3180
atgcctccca gagcttggtg tctccacttg tatatatggc tcagaggagt aaataatgg	3240
aaaagtaatc agcatatgtg taaagattta tacagttgaa aacttgtaat ttccccagg	3300
aggagaagaa gttttctggc gcagtggact gccacacaagcc accatgtaac ccctctcacc	3360
tgcctgcgt actggctgtg gaccaggtagg actcaagggtg gacgtgcgtt ctgccttcct	3420
tgttaatttt gtaataattt gagaagattt atgtcagcac acacttacag agcacaatg	3480
cagtatatac gtgctggatg tatgtaaata tattcaaattt atgtataat atatattata	3540
tatttacaag gagttttttt ttgttattgt tttaatggc tgcccaatg cacctagaaa	3600
attggctct cttttttaa tagtatttg ctaaatgttg ttcttacaca taatttctta	3660
attttcaccc agcagagggtg gaaaaatact tttgcttc gggaaaatgg tataacgtta	3720
atttattaaat aaattggtaa tataaaaaac aattaatcat ttatagttt ttttggtaatt	3780
taagtggcat ttctatgcag gcagcacagc agacttagtta atctattgtc tggacttaac	3840

-continued

tagttatcg atccttgaa aagagaatat ttacaatata tgactaattt gggaaaatg	3900
aagttttgat ttatggat ttaaaatgctg ctgtcagacg attgttctta gacccctaa	3960
atgccccata taaaagaac tcattcatag gaaggtgtt cattttggtg tgcaaccctg	4020
tcattacgtc aacgcacgt ctaactggac ttcccaagat aaatggtacc agcgtccct	4080
taaaagatgc ctttatccat tccttgagga cagacacctg ttgaaatgtat gcagaatgt	4140
gtttctctct ggcagctggc cttctgcctc tgagttgcac attaatcaga ttagectgt	4200
ttctcttcag tgaattttga taatggcttc cagactctt ggcgttggag acgcctgtt	4260
ggatcttcaa gtcccatcat agaaaattga aacacagagt tgttctgcgt atagtttgg	4320
ggatacgtcc atcttttaa gggattgctt tcatctaatt ctggcaggac ctcacaaaa	4380
gatccagcct catacctaca tcagacaaaa tatcgccgtt gttccctctg tactaaagta	4440
ttgtgttttg ctttgaaac acccactcac tttgcaatag ccgtgcaaga tgaatgcaga	4500
ttacactgtat cttatgtgtt acaaaattgg agaaaagtatt taataaaacc tgttaattt	4560
tatactgaca ataaaaatgt ttctacagat attaatgtt acaagacaaa ataaatgtca	4620
cgcaacttat tttttata aaaaaaaaaa aaaa	4654

<210> SEQ_ID NO 7

<211> LENGTH: 806

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile			
1	5	10	15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val			
20	25	30	

Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln			
35	40	45	

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro			
50	55	60	

Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly			
65	70	75	80

Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val			
85	90	95	

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg			
100	105	110	

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala			
115	120	125	

Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr			
130	135	140	

Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp			
145	150	155	160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys			
165	170	175	

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly			
180	185	190	

Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His			
195	200	205	

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly			
210	215	220	

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr

US 9,226,960 B2

49**50**

-continued

225	230	235	240
Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln			
245	250	255	
Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu			
260	265	270	
Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu			
275	280	285	
Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro			
290	295	300	
Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu			
305	310	315	320
Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu			
325	330	335	
Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala			
340	345	350	
Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu			
355	360	365	
Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe			
370	375	380	
Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu Arg Ser			
385	390	395	400
Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg			
405	410	415	
Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser			
420	425	430	
Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly			
435	440	445	
Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys			
450	455	460	
Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu			
465	470	475	480
Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys			
485	490	495	
Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp			
500	505	510	
Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met			
515	520	525	
Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala			
530	535	540	
Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys			
545	550	555	560
Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp			
565	570	575	
Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys			
580	585	590	
Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu			
595	600	605	
Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu			
610	615	620	
Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg			
625	630	635	640
Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu			
645	650	655	

-continued

Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr
660 665 670

His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
675 680 685

Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
690 695 700

Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705 710 715 720

His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
725 730 735

Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
740 745 750

Thr Val Thr Ser Thr Asp Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu
755 760 765

Gln Tyr Ser Pro Gly Gly Gln Asp Thr Pro Ser Ser Ser Ser Gly
770 775 780

Asp Asp Ser Val Phe Ala His Asp Leu Leu Pro Pro Ala Pro Pro Ser
785 790 795 800

Ser Gly Gly Ser Arg Thr
805

<210> SEQ ID NO 8
<211> LENGTH: 4304
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

gtcgccggca gctggcgcgg cgccgtcctg ctctgccggt cgcacggacg caccggccgg 60
ccggccggccg gagggacggg gccccggatgg ggcccgccgg aagcgagccg gagcgggagc 120
cgccgcgttagc gagccgggct ccggcgctcg ccagtctccc gagcggccgc cgcctccgc 180
cggtgcccgc gcccggccgt gggggccgc atgcccgcgc gcgctgcctg aggacgcgc 240
ggccccccgc cccgecatgg gcgcacctgc ctgcgcctc ggcgtctgcg tggccgtggc 300
catcgtggcc ggcgectctt cggagtccctt ggggacggag cagcgegtcg tggggcgagc 360
ggcagaagtc cccggccca agccccgeca gcaggagcag ttggcttcg gcagegggga 420
tgctgtggag ctgagctgtc cccggcccg gggtgtccca atggggccca ctgtctgggt 480
caaggatggc acagggctgg tgccctcgga ggcgtctcg gtggggccccc agcggctgca 540
gggtgctgaat gcctcccaacg aggactccgg ggcctacagc tgccggcagc ggctcacgca 600
gcccgtactg tgccacttca gtgtcggtt gacagacgct ccattctcg gagatgacga 660
agacggggag gacgaggactg aggacacagg tgtggacaca gggggccctt actggacacg 720
gcccggccg atggacaaga agctgctggc cgtggccggc gccaacacccg tccgcttccg 780
ctgcccagcc gctggcaacc ccactccctc catctctgg ctgaagaacg gcagggagtt 840
ccggccggag caccgcattt gaggcatcaa gctgcggcat cagcagtggc gcctggcat 900
ggaaagctgtg gtgcctcggt accggccaa ctacacctgc gtcgtggaga acaagttgg 960
cagcatccgg cagaactaca cgtggacgt gctggagcgc tcccccgcacc ggcccatccct 1020
gcaggccgggg ctgcccggca accagacggc ggtgctggc agcgcacgtgg agttccactg 1080
caaggtgtac agtgacgcac agccccacat ccagtggctc aagcacgtgg aggtgaatgg 1140
cagcaaggtg ggccggacg gcacacccta cgtaaccgtg ctcaagacgg cggccgtaa 1200

-continued

caccaccgac aaggagctag aggttctctc cttgcacaac gtcacccgg aggacgcgg	1260
ggagtagacacc tgcctgggg gcaattctat tgggtttct catcaactcg cgtggctgg	1320
ggtgctgcca gccgaggagg agctggtgg ggctgaecag gggggcagt tgatgcagg	1380
catcctcagc tacggggtgg gcttcttctt gttcatectg gtggggcgg ctgtgacgct	1440
ctggccgcgtc cgccggcccc ccaagaaagg cctgggtccccc acaggatctc	1500
ccgcgtcccg ctcaagcgac aggtgtccct ggagtccaaac gctccatga gctccaaac	1560
accactggtg cgcatcgcaa ggctgtctc agggggggc cccacgctgg ccaatgtctc	1620
cgagctcgag ctgcctggcc accccaaatgg ggagctgtct cggggccggc tgaccctgg	1680
caagccccctt gggggggct gttcgccca ggtggcatg gggggggcca tcggcatatga	1740
caaggaccgg gcccacaagc ctgtcacgt agccgtgaag atgctgaaag acgtgcac	1800
tgacaaggac ctgtcgacc tgggtgtctga gatggagatg atgaagatga tcggaaaca	1860
caaaaacatc atcaacctgc tggggccctg cacgcaggc gggccctgt acgtgctgg	1920
ggagtagacgcg gccaagggtt acctgcggga gttctgcgg gggggggc cccggggcct	1980
ggactactcc ttgcacacct gcaagccccc cgaggagcag ctcacccatc aggacctgg	2040
gtcctgtgcc taccagggtgg cccggggcat ggagacttgc gctcccaaga agtgcata	2100
caggggacctg gctgcccgc atgtgctggt gaccgaggac aacgtgatga agatgcaga	2160
cttcgggctg gcccgggacg tgacacaacct cgactactac aagaagacaa ccaacggcc	2220
gctgcccgtg aagtggatgg cgccgtggc cttgttgcg cgagtcata ctcaccagag	2280
tgacgtctgg tccttgggg tcctgctcg ggagatcttc acgctgggg gctcccgta	2340
ccccggcata cctgtggagg agctttcaa gctgctgaag gggggccacc gcatggacaa	2400
gcccggcaac tgcacacacg acctgtacat gatcatgcgg ggtgtgcgc atgcccgc	2460
ctcccgagg cccacccatc agcagctggt ggaggacctg gaccgtgtcc ttaccgtac	2520
gtccaccggc gagtaacctgg acctgtcgcc gccttcgag cagtaactccc cgggtggca	2580
ggacacccccc agctccagct cctcaggggc cgactccgtg tttgcccacg acctgtgcc	2640
ccccggggca cccagcgtg ggggtcgcc gacgtgaagg gcaactggc cccaaatgg	2700
tgaggggtcc ttagcagccc acctgtctgc tgggtcacag ccactcccg gcatgagact	2760
cagtgcacatc ggagagacag ctacacagag ctttgtctg tgggtgtgtg tgggtgtgt	2820
tgtgtgtgtg tggcacatc cgctgtgtcc tgggtgtgtg cgcatcttc ctccagggtc	2880
agaggttacc tgggtgtccc cgctgtgtg caacgggtcc ctgactgggt ctgcagcacc	2940
gagggggctt tgggtgggg ggacccagtg cagaatgtaa gtggggccac cgggtggac	3000
ccccgtgggg caggaggctg gggccgacat ggctccggcc tctgccttgc caccacggg	3060
catcacaggg tgggtctgg cccctccac acccaaagct gggccgtcc ggaagccca	3120
catgtccacg accttgtgcc tgggtgttta gttgcacccg ctcacccatc ccaggcttc	3180
ccacttccca ccctggccct cagagactga aattacgggt acctgaagat gggagcc	3240
acctttatc caaaagggtt attccggaaa ctgtgtaca tttctataaa tagatgtgt	3300
gtatatggta tatatacata tatataatata acatataatgg aagaggaaaa ggctggtaca	3360
acggaggccct ggcacccctgg gggcacagga ggcaggcatg gcccggccgg gggcgtggg	3420
gggcgtggag ggaggccccca ggggtctca cccatgcac gaggacca gggcccttc	3480
tggcaccgcgat tttttttttt aaaactggac ctgttatattt gtaaagctat ttatggccc	3540
ctggcactct tggccacaca ccccaacact tccagcattt agctggccac atggcggaga	3600

-continued

```

gttttaattt ttaacttattt gacaaccgag aaggtttatac ccggccgatag agggacggcc 3660
aagaatgtac gtccagcctg ccccgagct ggaggatccc ctccaagcct aaaaggttgt 3720
taatagttgg aggtgattcc agtgaagata tttatttcc tttgtcttt ttcaggagaa 3780
ttagatttct ataggatttt tctttaggag atttattttt tggacttcaa agcaagctgg 3840
tattttcata caaattcttc taattgctgt gtgtcccagg cagggagacg gtttccaggg 3900
aggggcggc cctgttgca ggttcccgatg ttatttagatg ttacaagttt atatatatct 3960
atatatataa tttatttgagt tttacaaga tgtattttgtt gtagacttaa cacttcttac 4020
geaatgcttc tagagttta tagctggac tgctacctt caaagctgg agggaaagccg 4080
tgaattcagt tggttcgttc tgtactgtta ctggccctg agtctggca gctgtccctt 4140
gttgcctgc agggccatgg ctcagggtgg tctcttctt gggcccagtg catggtggcc 4200
agaggtgtca cccaaaccgg caggtgcgt tttgttaacc cagcgcacgaa cttccgaaa 4260
aataaaagaca cctgggtgct aacctggaaa aaaaaaaaaa aaaa 4304

```

<210> SEQ ID NO 9
<211> LENGTH: 762
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

```

Met Arg Leu Leu Ala Leu Leu Gly Val Leu Leu Ser Val Pro Gly
1 5 10 15

Pro Pro Val Leu Ser Leu Glu Ala Ser Glu Glu Val Glu Leu Glu Pro
20 25 30

Cys Leu Ala Pro Ser Leu Glu Gln Gln Glu Leu Thr Val Ala
35 40 45

Leu Gly Gln Pro Val Arg Leu Cys Cys Gly Arg Ala Glu Arg Gly Gly
50 55 60

His Trp Tyr Lys Glu Gly Ser Arg Leu Ala Pro Ala Gly Arg Val Arg
65 70 75 80

Gly Trp Arg Gly Arg Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala
85 90 95

Gly Arg Tyr Leu Cys Leu Ala Arg Gly Ser Met Ile Val Leu Gln Asn
100 105 110

Leu Thr Leu Ile Thr Gly Asp Ser Ser Thr Ser Ser Asn Asp Asp Glu
115 120 125

Asp Pro Lys Ser His Arg Asp Leu Ser Asn Arg His Ser Tyr Pro Gln
130 135 140

Gln Ala Pro Tyr Trp Thr His Pro Gln Arg Met Glu Lys Lys Leu His
145 150 155 160

Ala Val Pro Ala Gly Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly
165 170 175

Asn Pro Thr Pro Thr Ile Arg Trp Leu Lys Asp Gly Gln Ala Phe His
180 185 190

Gly Gly Asn Arg Ile Gly Gly Ile Arg Leu Arg His Gln His Trp Ser
195 200 205

Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys
210 215 220

Leu Val Glu Asn Ala Val Gly Ser Ile Arg Tyr Asn Tyr Leu Leu Asp
225 230 235 240

Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro

```

US 9,226,960 B2

57**58**

-continued

245	250	255
Ala Asn Thr Thr Ala Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys		
260	265	270
Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Ile Val		
275	280	285
Ile Asn Gly Ser Ser Phe Gly Ala Asp Gly Phe Pro Tyr Val Gln Val		
290	295	300
Leu Lys Thr Ala Asp Ile Asn Ser Ser Glu Val Glu Val Leu Tyr Leu		
305	310	315
Arg Asn Val Ser Ala Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly		
325	330	335
Asn Ser Ile Gly Leu Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro		
340	345	350
Gly Thr Gly Arg Ile Pro His Leu Thr Cys Asp Ser Leu Thr Pro Ala		
355	360	365
Gly Arg Thr Lys Ser Pro Thr Leu Gln Phe Ser Leu Glu Ser Gly Ser		
370	375	380
Ser Gly Lys Ser Ser Ser Leu Val Arg Gly Val Arg Leu Ser Ser		
385	390	395
Ser Gly Pro Ala Leu Leu Ala Gly Leu Val Ser Leu Asp Leu Pro Leu		
405	410	415
Asp Pro Leu Trp Glu Phe Pro Arg Asp Arg Leu Val Leu Gly Lys Pro		
420	425	430
Leu Gly Glu Gly Cys Phe Gly Gln Val Val Arg Ala Glu Ala Phe Gly		
435	440	445
Met Asp Pro Ala Arg Pro Asp Gln Ala Ser Thr Val Ala Val Lys Met		
450	455	460
Leu Lys Asp Asn Ala Ser Asp Lys Asp Leu Ala Asp Leu Val Ser Glu		
465	470	475
Met Glu Val Met Lys Leu Ile Gly Arg His Lys Asn Ile Ile Asn Leu		
485	490	495
Leu Gly Val Cys Thr Gln Glu Gly Pro Leu Tyr Val Ile Val Glu Cys		
500	505	510
Ala Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro		
515	520	525
Gly Pro Asp Leu Ser Pro Asp Gly Pro Arg Ser Ser Glu Gly Pro Leu		
530	535	540
Ser Phe Pro Val Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met		
545	550	555
Gln Tyr Leu Glu Ser Arg Lys Cys Ile His Arg Asp Leu Ala Ala Arg		
565	570	575
Asn Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly		
580	585	590
Leu Ala Arg Gly Val His His Ile Asp Tyr Tyr Lys Lys Thr Ser Asn		
595	600	605
Gly Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg		
610	615	620
Val Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Ile Leu Leu Trp		
625	630	635
Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu		
645	650	655
Glu Leu Phe Ser Leu Leu Arg Glu Gly His Arg Met Asp Arg Pro Pro		
660	665	670

-continued

His	Cys	Pro	Pro	Glu	Leu	Tyr	Gly	Leu	Met	Arg	Glu	Cys	Trp	His	Ala
675				680				685							
Ala	Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys	Gln	Leu	Val	Glu	Ala	Leu	Asp
690				695				700							
Lys	Val	Leu	Leu	Ala	Val	Ser	Glu	Tyr	Leu	Asp	Leu	Arg	Leu	Thr	
705				710			715			720					
Phe	Gly	Pro	Tyr	Ser	Pro	Ser	Gly	Gly	Asp	Ala	Ser	Ser	Thr	Cys	Ser
725				730			735								
Ser	Ser	Asp	Ser	Val	Phe	Ser	His	Asp	Pro	Leu	Pro	Leu	Gly	Ser	Ser
740				745			750								
Ser	Phe	Pro	Phe	Gly	Ser	Gly	Val	Gln	Thr						
755				760											

<210> SEQ ID NO 10

<211> LENGTH: 2418

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

agtccagctt	gggtccctga	gagctgttag	aaggagatgc	ggctgtgtct	ggccctgttg	60
gggggtctgc	ttagtgtgcc	tgggcctcca	gttttgtccc	tggaggcctc	tgaggaagtg	120
gagctttagc	cctgccttgc	tcccaagcctg	gagcagcaag	agcaggagct	gacagtagcc	180
cttgggcagc	ctgtgcggct	gtgtgttgcc	cgggctgagc	gtgggtggcca	ctggtaacaag	240
gaggggcagtc	gcctggcacc	tgctggccgt	gtacggggct	ggagggggccg	cctagagatt	300
gccagettcc	tacctgagga	tgctggccgc	tacctctgcc	tggcacgagg	ctccatgatc	360
gtcctgcaga	atctcacctt	gattacaggt	gactcctcg	cctccagcaa	cgatgtgag	420
gaccccaagt	cccatagggaa	cctctcgaa	aggcacagtt	acccccagca	agcacccctac	480
ttggacacacc	cccagcgcatt	ggagaagaaa	ctgcacatgc	tacctgcggg	gaacaccgtc	540
aagttccgt	gtccagctgc	aggcaacccc	acgcccacca	tccgctggt	taaggatgga	600
caggccatttc	atggggggaa	ccgcatttgg	ggcatteggc	tgcgcacatca	gcactggagt	660
ctcgtgtatgg	agagegtgg	gccctcgac	cgccggcacat	acacctgcct	ggtagagaac	720
gctgtgggca	gcateccgta	taactacctg	ctagatgtc	tggageggc	cccgeacccg	780
cccatectgc	aggccgggct	cccgccaaac	accacagecg	tggtgggcag	cgacgtggag	840
ctgctgtgc	aggtgtacag	cgtatcccc	ccccacatcc	agtggctgaa	gcacatcg	900
atcaacggca	gcagcttcgg	agccgacggt	ttcccctatg	tgcaagtcc	aaagactgca	960
gacatcaata	gctcagaggt	ggaggctctg	tacctgcgg	acgtgtcagc	cgaggacgca	1020
ggcgagtaca	cctgcctcgc	aggcaattcc	atcgccctct	cctaccatgc	tgcctggctc	1080
acgggtgtgc	caggtaactgg	gcccattcccc	cacctcacat	gtgacagcct	gactccagca	1140
ggcagaacca	agtctcccac	tttgcagttc	tccctggagt	caggctcc	cgccaagtca	1200
agtcatccc	tggtacgagg	cgtgcgtctc	tcctccagcg	gccccgcctt	gctcgccggc	1260
ctcgtgtatgg	tagatctacc	tctcgaccca	ctatggaggt	tcccccggga	caggctggtg	1320
cttgggaagc	cccttagggcga	gggctgtctt	ggccaggtag	tacgtgcaga	ggcccttggc	1380
atggaccctg	cccgccctga	ccaagccagc	actgtggcc	tcaagatgct	caaagacaac	1440
gcctctgaca	aggacctggc	cgacactggc	tccggagatgg	aggtgtatgaa	gctgtacggc	1500
cgacacaaga	acatcatcaa	cctgcttggt	gtctgcaccc	aggaagggcc	cctgtacgt	1560

-continued

atcgtggagt gcgccgcca gggaaacctg cgggagttcc tgcgggcccc ggcggccca	1620
ggcccccggacc tcagccccga cggtcctcgg agcagtggagg ggccgccttc cttcccaagtc	1680
ctggtctcct gcgcctacca ggtggcccgaa ggcatgcagt atctggagtc ccggaagtgt	1740
atccacccggg acctggctgc ccgcaatgtg ctggtgactg aggacaatgt gatgaagatt	1800
gctgactttg ggctggcccg cggcgctccac cacattgact actataagaa aaccagcaac	1860
ggccgcgtgc ctgtgaagtg gatggcgccc gagggcttgg ttgaccgggt gtacacacac	1920
cagagtgacg tgtggtcttt tgggatcctg ctatggaga tcttcaccct cgggggctcc	1980
ccgtatccctg gcatacccggt ggaggagctg ttctcgctgc tgccggaggg acatcgatg	2040
gaccgacccc cacactgccc cccagagctg tacgggctga tgcgtgagtg ctggcacgca	2100
gccccctccc agaggcctac cttcaagcag ctggtgagg cgctggacaa ggtcctgctg	2160
gccgtctctg aggagtaccc cgacccctcg ctgacccctcg gaccctatcc cccctctgg	2220
ggggacgcca gcagcacctg ctccctccagc gattctgtct tcagccacga cccctgcca	2280
ttgggatcca gctccctccc ctccgggtct ggggtgcaga catgagcaag gctcaaggct	2340
gtgcaggcac ataggctggt ggccttgggc cttggggctc agccacagcc tgacacagtg	2400
ctcgacccctg atagcatg	2418

<210> SEQ_ID NO 11

<211> LENGTH: 155

<212> TYPE: PRT

<213> ORGANISM: Bos taurus

<400> SEQUENCE: 11

Met Ala Ala Gly Ser Ile Thr Thr Leu Pro Ala Leu Pro Glu Asp Gly			
1	5	10	15

Gly Ser Gly Ala Phe Pro Pro Gly His Phe Lys Asp Pro Lys Arg Leu			
20	25	30	

Tyr Cys Lys Asn Gly Gly Phe Phe Leu Arg Ile His Pro Asp Gly Arg			
35	40	45	

Val Asp Gly Val Arg Glu Lys Ser Asp Pro His Ile Lys Leu Gln Leu			
50	55	60	

Gln Ala Glu Glu Arg Gly Val Val Ser Ile Lys Gly Val Cys Ala Asn			
65	70	75	80

Arg Tyr Leu Ala Met Lys Glu Asp Gly Arg Leu Leu Ala Ser Lys Cys			
85	90	95	

Val Thr Asp Glu Cys Phe Phe Glu Arg Leu Glu Ser Asn Asn Tyr			
100	105	110	

Asn Thr Tyr Arg Ser Arg Lys Tyr Ser Ser Trp Tyr Val Ala Leu Lys			
115	120	125	

Arg Thr Gly Gln Tyr Lys Leu Gly Pro Lys Thr Gly Pro Gly Gln Lys			
130	135	140	

Ala Ile Leu Phe Leu Pro Met Ser Ala Lys Ser			
145	150	155	

<210> SEQ_ID NO 12

<211> LENGTH: 6601

<212> TYPE: DNA

<213> ORGANISM: Bos taurus

<400> SEQUENCE: 12

cggggccgc gccgcggagc gcgtcgagg ccggggccgg ggcgcggccg ctcccccgc 60

ggctccaggc gctcggggac cccgcacaggc cttgggtggc gccatggccg ccggagcat 120

-continued

caccacgctg ccagccctgc cggaggacgg cggcagcggc gtttcccgc cggccactt	180
caaggacccc aagcggttgt actgcagaagaa cgggggttc ttccctgcgc tccacccga	240
cggccgagtgc acgggggtcc gcgagaagag cgacccacac atcaaactac aacttcaagc	300
agaagagaga ggggttgtgt ctatcaaagg agtgtgtgca aaccgttacc ttgctatgaa	360
agaagatgga agattactag cttctaaatg tgttacagac gagtgttct ttttgaacg	420
attggagtct aataactaca atacttacgg gtcaaggaaa tactccagtt ggtatgtggc	480
actgaaacga actgggcagt ataaaacttgg accaaaaaca ggacctggc agaaagctat	540
actttttctt ccaatgtctg ctaagagctg atcttaatgg cagcatctga tctcattta	600
catgaagagg tatatttcag aaatgtgtta atgaaaaaag aaaaatgtgt acagttagct	660
getcagtttggtaactgtt cagataacccg tttatctaag agtaaaatata ttaaccattt	720
ccttagttttttttaaaga aaaaacacaa taacagcaaa aattcctgga aatgtatac	780
atttccactt ttatatacgc atttccctttt atccagtgaa acttacttaa agctacaatc	840
tttcatacag ttgcttcatt tgaagaggot tttaaaatgt gtacaaacaa gtttcttca	900
tggaaattat agacattttaga aaattaaagt catattttagt tattaaccca aatgtccact	960
acttcctata atatggcaca cattaatcta catgtacaac ttacttaaac atgtacaact	1020
tacttaaaca ttttaaaaac atgtaaaatat gaatttaatc cattcctgtc atagtttgt	1080
aattgtctgg cagtttcttg tgatagagtt tatagaacaa gctgtgtaa actgtggca	1140
gttctccat ggtcagatca attttgtcaa acccttctt gtacccatatac agcagcagcc	1200
ttgcaactct gcttggatgtt gggatcgat ttttagtctt gactagatcg ctgagattca	1260
tccactcaca cttaaagcat tcacgctggc aaaaatttat ggtgaatgaa tatggcttta	1320
agcggcagat aatatacata tctgacttcc caaaagctcc tggatgggtg tgctgttgc	1380
gaataactcag gagggatctg aattcggatt ttataccagt ctcttcaaaa acttctcgaa	1440
ctgctgtatc tcctacataa aagaaaatgt acaaataat aacgattata cttttagaaa	1500
tttaatcaa gatttcaga taagaaagca ttattatgtt aagattcaaa agttaaaaat	1560
ttacccttaag aaaagaaagc tttccctgtt aactctgtcc tctggacatc ctgaaaaaac	1620
aaagtattttt cttaccactg tatagctaa aagcttttga aataatattt ctggcttc	1680
tacttgcag cttaccatc tatataatgt tattttggta gtcacatatt tttaatct	1740
tcctgcttta tttccaaaaa gttaatattt ctgtatattt ttccattttt atcttgtcc	1800
tgattatcca taaaactgc ctaaactgtat aaacattga agtaagaaaa agtgcatt	1860
tcttctttac aaaagtctgt agagctgcag aatataataga actaggaaat gattcaatc	1920
atccctggc tctctggta ctgtcaggcc tctgaagtca taggtcggtt ttgcgtataa	1980
ccattttgtt atgccttctt agttattctg tcagtgaaat cccaccatgg taatttctgg	2040
cattttctttt gtttcttgct gtttcaaaga acttggattt attcttctaa cacaaaatg	2100
ctacagtcat cagaagtttta aaaaaaaact tgcaatttac agaattttat aatattacca	2160
ggctttcac attttataaa gttgatttttt aaataatatg caaatttcta ggacaggatt	2220
tttattgcca ttaacttattttt tttgtggctg ctcttctaa atatccagat gaaccctcta	2280
cctgggattt ctgtatattt ctgtatgtt cattgtctcc caaagtgttt atgaaaagcc	2340
ctaaaaaaagc tgccttcctt gtcttatttcc tggaaagttt cacaattgcc acaagtatag	2400
atttttgttt aaatatcttt taatgccttc attttcttg tttgtcagggtt gtaaaactgta	2460

-continued

tttggcttct cagtagtcct gctagtgagg aataggcaag gaagagcaag taaaacaagaa	2520
atgttgcagt gtttttcta ataacagtc tggaaataag cacaggaaga gtatgtgta	2580
aaatatgaca tctgtctacc atatttgaat tctgtgtgaa cgaactttt aattgagatt	2640
tgctaaagat caaatcaaca tggttagaaa ttatatttt aaactgaaaa tatagaaaaa	2700
tatatgttaa gaaaaggaaa acttggctta agaaaaataa ttttttgtt attaaaaaac	2760
ttgttattaag ttgttacag attgtggcac tagtcttaaa ttttacatgt catttgctga	2820
tctgacttaa aaattgttca aatgtttaaa aagttctta aacatttaa aatgaccatg	2880
ggatcttgt ttagctctta ataacactag tcaagagttt aacatTTTtgc tccatTTTtgc	2940
gcctgtttg tatgttataag aagcacagga tggggctggt gagtgaatct gcaggctta	3000
gccccatccca cagcagctga ttccaaatca gcactgcctg gatagttga tccatTTTtgc	3060
ttgaatcatg atgtcattaa cttagattaa aattaaatgg gcaaataagt gcttttagat	3120
ctagaggaac caaccccttc tatattaaaa ttgaaatctc ttctccaagg attttatgtat	3180
gaattaaaaa tttaattta ggtaaagtgc gttatttgct ggtattttt taaatgtact	3240
gtaaatcaccc tgaataacgg ttttatgtat ttgaaataa taggaaaaacc aagagggttt	3300
tgtttttattt ttgtgtgtt gaaagatgtt taaaacatc atagtgtttt atttatgtaa	3360
aggacagttttc taaaaatggag tttatatttgc ttacttctat ttgtatata ttaataacag	3420
gatttagtttgc aataaaaaata ataggaaaaa ctgtgcagaa tgtggatttt cctgggtgtct	3480
ccccctcaact ctggtaact gatgagctct ggcggccccc cactgttttgc cagacctttg	3540
gtatacagg gagttctctt cctgttagtg ctaatgatgat tttccccccc ccagaaaggc	3600
agtttgcgtt tttaacctta tctatagata ggcttatcg gagaaggcaat ggcacccac	3660
tccagaactc ttgcctggaa aatccatgg atggaggagc ctgggtggct gcagtccatg	3720
gggtcgctaa gagttggaca cgactgagcg acttcacttt cacttttgc tttcatgc	3780
tggagaagga aatggcaacc cactccggtg ttctgcctg gagaatccgg gggacgaggg	3840
agcctggta gctgtgtct atggggtcgc agagtcggac atgactgaag tgacttagca	3900
gcagcataga taccttttg tactctgtt catttaccta atacttatca aagaatgaag	3960
gattccaaac aaatgagctt cttatTTTta ctgtattta ctgtttttttttaa cccatgtga	4020
acatttgcac atttatgtat gcggcagtc tattacatac tttcctaaaa acagatTTTta	4080
aagaaaaataa ataattcctg gttgatttgctt cttcatcatt aagagtaatc tattactata	4140
ctgttacaaa acagaaatgt actctacata gacatggctt ttcagatctc tatgtcttttgc	4200
atcatttcta gctgtttca gagttttatc acttctgagg caatgtttca gtttttctta	4260
ctccttaggca atatggtaaa tgccagttgc tgcttttttca ttaattccat gtggctggag	4320
gcattaaaaa caatctctga cttaggtgggt tggatTTTta cccacaagta tttttaaaaa	4380
gtatgttaattt tctatTTTta tggacttggaa atgttctggaa gtacactcaa acctaaatgt	4440
tacttattta catgggtggaa aaatgtgtttt atttacattt aaatataatct gaaattcaga	4500
atataatgttca aactcaaat gaaaaaaatgtt attcatttgc aagaaaaaaa aaaaaaaatgt	4560
tattcatttgc aagggcaag gttcagaaga ggaagttata caaacttcct atagactgct	4620
atttgcacccag tatggatttag ataaggatgt aaaacagaca cttactagt tcacatgtat	4680
tcataatcaca tgatgtgtg agataaccgg gaattctaga gtatgtgtt ttttttttca	4740
gcactggcac tactacaaa tccttttttca aacacagaag acctaggaa gactaagcta	4800
aagggtcagtg agcaccctaaa aacccaaaatc tgctatgtata tatttgcgtt gaaatTTTta	4860

-continued

tat	taggatgt taggagttgg ctgtatacta caaataggac atttcatct gtggAACATT	4920
aaaaaaaat	catttcaagt atatatatat acatTTAAA ataatttagg gcactgcTTT	4980
catatTTATG	atggctaaag agaataggGT acatatacac agtgaggaca aagtcatAGA	5040
aaaatAGTTA	agtatgAAAT gagttatCTA ttgattttt atgataAGGA ctgtgcCTGA	5100
cacaatGGTT	taaggaAGAG acaggAAAAC tcaatttCTA ctctcgATTt CCTGtaAAAT	5160
cagtgcAAAG	gaattctTAG atttttCAA acttccCTTA gataCTGAGC tcagtAAATT	5220
gttcttagAA	attatCTCTC atttcAGACT ttctcacATG agacatGTTA ccatTTTG	5280
gcttctgAC	tatcgAAAAA aatagATAAA atttCCATAA acagaAGAAAT tataACCACCA	5340
ctgttcaATA	attgcTTTA aaatATTTCA cattTCATT AAAAGTTCTC ttcaACCTTG	5400
tgatTTAAATG	gtcaAGAAATT tttCTAAATAG taaAGTTCCA ACAATTTGT tatGCCGAGT	5460
tgctcAGTTG	tgtctgACTC ttgtgACTCC atggACTGTA gcccACCCAGG ctcttCTGTC	5520
catggggATT	ctccaggCAA gaataCTGGA gtgggttgCC atGCCCTCCT ccaggGGATA	5580
tttccaACCA	agggatCAA CCCAGGTCTC cctcATTGTA ggcAGATTCT taattGTCTG	5640
acctaccAGG	gaaACCTCC aacaATTTA gtcaaATTCA aaatATCCCT taatGCTAAC	5700
cttaactGTa	tatccAAAGT ttctcATTTC caaATTATCT agaAGCAGTC ctaAGCCAAA	5760
aaacaggGTGT	tatgctCTGA atggTATTAT ttataCTAAT ggaATAAAATT gtatGTTAA	5820
gttttgcTAT	taatTTTATA tcagcACTGA ataacttCTT tgaaATTTC tgacttagTC	5880
taaaccAAATT	agaaAGTGTa aaatCTCATT ctcaGCTCTA gAGCAAGAAA gtaAAACACAT	5940
aaatTTATTTC	agcATTTCa agtcaATTAT aaatATAAA gataCCACCC aataTCTTCT	6000
ccaggGCTCTG	acaggGCTCC ttggAACTTC cacatGTTT tcagCTGTag tattAAATCA	6060
gaaAGCAAAG	ttaaacACAGC tcttATTTCAC taacataCAC atacGTAGAG atGCCACAGA	6120
agctaccACAT	aattgtatCAA ggtgggttag aattttTTTT ttCGTAACTG ccACCAATT	6180
ttttcagCTT	ccttcotCAC tcctttCTTC tctcGGAAA ctgctGACTT gtgAAATCTT	6240
tcctatTTT	ttatTTAGGA aatAGAAGTG gtttttttTA tgTTAATGTG ataaATCTG	6300
tatgagtGAA	acagtGGGGG gaacatCTAC tgaatttGTA tagTTAAAAT ttttgcTGC	6360
tagTTATTAA	aagaataCAT gaatCTTACT gatGCTGCTA taaATTAGTA gaaaATATAT	6420
aaatgtAAATC	actaaAGTAT gctatTTTA attttcaATT tactTTCTAT attGtGtGTC	6480
taatcAgATA	tattaATCTT aagAGTTTC ttgttCTCTG tgTTAATGAT tttatGTA	6540
aatataATTG	tcttccTGG gaagtGTGAA taaaATTGAT ttaagTTCT ggctaaaaAA	6600

<210> SEQ ID NO 13
<211> LENGTH: 820
<212> TYPE: PRT
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 13

Met	Trp	Ser	Arg	Lys	Cys	Leu	Leu	Phe	Trp	Ala	Val	Leu	Val	Thr	Ala
1				5					10					15	

Thr Leu Cys Thr Ala Lys Pro Ala Pro Thr Leu Pro Glu Gln Ala Gln
20 25 30

Pro Trp Gly Ala Pro Val Glu Val Glu Ser Leu Leu Val His Pro Gly
35 40 45

Asp Leu Leu Gln Leu Arg Cys Arg Leu Arg Asp Asp Val Gln Ser Ile

-continued

50	55	60
Asn Trp Leu Arg Asp Gly Val Gln Leu Ala Asp Ser Asn Arg Thr Arg		
65	70	75
Ile Thr Gly Glu Glu Val Val Arg Gly Ser Val Pro Ala Asp Ser		
85	90	95
Gly Leu Tyr Ala Cys Val Thr Ser Ser Pro Ser Gly Ser Asp Thr Thr		
100	105	110
Tyr Phe Ser Val Asn Val Ser Asp Ala Leu Pro Ser Ser Glu Asp Asp		
115	120	125
Asp Asp Asp Asp Asp Ser Ser Ser Glu Glu Lys Glu Thr Asp Asn Thr		
130	135	140
Lys Pro Asn Pro Val Ala Pro Tyr Trp Thr Ser Pro Glu Lys Met Glu		
145	150	155
160		
Lys Lys Leu His Ala Val Pro Ala Ala Lys Thr Val Lys Phe Lys Cys		
165	170	175
Pro Ser Ser Gly Thr Pro Asn Pro Thr Leu Arg Trp Leu Lys Asn Gly		
180	185	190
Lys Glu Phe Lys Pro Asp His Arg Ile Gly Gly Tyr Lys Val Arg Tyr		
195	200	205
Ala Thr Trp Ser Ile Ile Met Asp Ser Val Val Pro Ser Asp Lys Gly		
210	215	220
Asn Tyr Thr Cys Ile Val Glu Asn Glu Tyr Gly Ser Ile Asn His Thr		
225	230	235
240		
Tyr Gln Leu Asp Val Val Glu Arg Ser Pro His Arg Pro Ile Leu Gln		
245	250	255
Ala Gly Leu Pro Ala Asn Lys Thr Val Ala Leu Gly Ser Asn Val Glu		
260	265	270
Phe Met Cys Lys Val Tyr Ser Asp Pro Gln Pro His Ile Gln Trp Leu		
275	280	285
Lys His Ile Glu Val Asn Gly Ser Lys Ile Gly Pro Asp Asn Leu Pro		
290	295	300
Tyr Val Gln Ile Leu Lys Thr Ala Gly Val Asn Thr Thr Asp Lys Glu		
305	310	315
320		
Met Glu Val Leu His Leu Arg Asn Val Ser Phe Glu Asp Ala Gly Glu		
325	330	335
Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu Ser His His Ser Ala		
340	345	350
Trp Leu Thr Val Leu Glu Ala Leu Glu Glu Arg Pro Ala Val Met Thr		
355	360	365
Ser Pro Leu Tyr Leu Glu Ile Ile Tyr Cys Thr Gly Ala Phe Leu		
370	375	380
Ile Ser Cys Met Val Gly Ser Val Ile Ile Tyr Lys Met Lys Ser Gly		
385	390	395
400		
Thr Lys Lys Ser Asp Phe His Ser Gln Met Ala Val His Lys Leu Ala		
405	410	415
Lys Ser Ile Pro Leu Arg Arg Gln Val Thr Val Ser Ala Asp Ser Ser		
420	425	430
Ala Ser Met Asn Ser Gly Val Leu Leu Val Arg Pro Ser Arg Leu Ser		
435	440	445
Ser Ser Gly Thr Pro Met Leu Ala Gly Val Ser Glu Tyr Glu Leu Pro		
450	455	460
Glu Asp Pro Arg Trp Glu Leu Pro Arg Asp Arg Leu Val Leu Gly Lys		
465	470	475
480		

-continued

Pro Leu Gly Glu Gly Cys Phe Gly Gln Val Val Leu Ala Glu Ala Ile
485 490 495

Gly Leu Asp Lys Asp Arg Pro Asn Arg Val Thr Lys Val Ala Val Lys
500 505 510

Met Leu Lys Ser Asp Ala Thr Glu Lys Asp Leu Ser Asp Leu Ile Ser
515 520 525

Glu Met Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn
530 535 540

Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu Tyr Val Ile Val Glu
545 550 555 560

Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu Gln Ala Arg Arg Pro
565 570 575

Pro Gly Leu Glu Tyr Cys Tyr Asn Pro Ser His His Pro Glu Glu Gln
580 585 590

Leu Ser Ser Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly
595 600 605

Met Glu Tyr Leu Ala Ser Lys Cys Ile His Arg Asp Leu Ala Ala
610 615 620

Arg Asn Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe
625 630 635 640

Gly Leu Ala Arg Asp Ile His His Ile Asp Tyr Tyr Lys Lys Thr Thr
645 650 655

Asn Gly Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp
660 665 670

Arg Ile Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu
675 680 685

Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Val Pro Val
690 695 700

Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro
705 710 715 720

Ser Asn Cys Thr Asn Glu Leu Tyr Met Met Met Arg Asp Cys Trp His
725 730 735

Ala Val Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu
740 745 750

Asp Arg Ile Val Ala Leu Thr Ser Asn Gln Glu Tyr Leu Asp Leu Ser
755 760 765

Met Pro Leu Asp Gln Tyr Ser Pro Ser Phe Pro Asp Thr Arg Ser Ser
770 775 780

Thr Cys Ser Ser Gly Glu Asp Ser Val Phe Ser His Glu Pro Leu Pro
785 790 795 800

Glu Glu Pro Cys Leu Pro Arg His Pro Ala Gln Leu Ala Asn Gly Gly
805 810 815

Leu Lys Arg Arg
820

<210> SEQ ID NO 14

<211> LENGTH: 3400

<212> TYPE: DNA

<213> ORGANISM: Bos taurus

<400> SEQUENCE: 14

```
ggctccgcga gtcagcttgc aaaggaggat cgagccccacg gcggagtcctc catggagggtg      60
tggagcctgg tcaccaacct ctaaccgcag aactggatg tggagccgga agtgtctct      120
```

-continued

cttctgggcc	gtgctggtca	cagecacgct	ctgcactgcc	aagccggccc	cgaccttgcc	180
ggagcaagcc	cagccctggg	gagcccctgt	ggaagtggag	tccctctgg	tccaccccg	240
tgacctgctg	cagctccgct	gtcggctgct	ggacgatgtt	cagagcatca	actggctcg	300
ggacggggtg	cagctggcg	acagcaaccg	cacgcgcac	accggggagg	aggtggaggt	360
tccggggtcc	gtgcccgg	actcaggct	ctacgcctgc	gtgaccagca	gcccctccgg	420
cagtgcacacc	acctacttct	ccgtcaaeagt	ctcagatgct	ctccctctgt	cggaggacga	480
tgatgacgac	gatgactct	cttcggagga	gaaggaaaca	gataaacacca	aaccaaacc	540
cgtggctccg	tactggacgt	caccagaaaa	gatggaaaag	aaactgcacg	cagtgccacg	600
tgccaagaca	gtgaagttca	aatgccctc	cagtggacc	ccgaacccca	cactgcgt	660
gctgaaaac	ggcaaagaat	tcaagccga	ccacaggatc	ggaggctaca	aggtccgtta	720
tgccacactgg	agcatcatta	tggactccgt	ggtgcctcg	gataagggca	actacacctg	780
catcgtggag	aacgaatacg	gcagcatcaa	ccatacctac	cagcttgatg	ttgtggagcg	840
gtccccctac	cggcccatec	tgccaggccgg	cttgccagcc	aacaagacgg	tggccctggg	900
cagcaacgtg	gagttcatgt	gcaaggtgta	cagtgcaccc	cagccccaca	tccagtggct	960
gaagcacatt	gaggtgaacg	ggagtaagat	tggccggac	aacctgcctt	atgtccagat	1020
cttgaagacg	gccggagtt	acaccaccga	caaagagatg	gaggtgctgc	acttaaggaa	1080
tgtctcttt	gaggacgcgg	ggggagtatac	atgcttggcg	ggtaactcta	tcggactctc	1140
ccatcactct	gcatggctga	ccgttctgga	agccctggaa	gagagacccg	cggtgatgac	1200
ttcgccgctg	tacctggaga	tcatcatcta	ttgcacgggg	gccttcctca	tctcctgcat	1260
ggtggggct	gtcatcatct	acaagatgaa	gagccgcaca	aagaagagtg	acttccacag	1320
ccagatggcc	gtgcacaagc	tggccaaagag	catccctctg	cgcagacagg	taacagtgtc	1380
ggetgactcc	agcgcgtcca	tgaactccgg	ggtcctgcta	gttcggccct	cgcgtctctc	1440
ctccagccgc	acccctatgc	tggccggggt	ctctgaatat	gagcttcccg	aagaccctcg	1500
ctggagctg	cctcgggaca	gactggttt	aggcaagccc	ctggagagg	gctgcttgg	1560
gcaggggtgt	ctggccggagg	ccatcggtct	ggacaaggac	agacccaacc	gtgtgaccaa	1620
agtggccgtg	aagatgctga	agtcggatgc	aacagagaaa	gacctgtcg	acctgatctc	1680
cgagatggag	atgatgaaga	tgattggaaa	acacaagaac	atcatcaatc	tgctggggc	1740
ctgtacacag	gatggccct	tgtatgtcat	cgtggagta	gcctccaagg	gcaatctcg	1800
agagtacctg	cagggccgga	ggccggccagg	gctggagta	tgctacaacc	ccagccacca	1860
ccccgaggag	cagctctct	ccaaggacct	ggtgtctgc	gcctaccagg	tggcccgagg	1920
catgggat	cttgcetcca	agaagtgcat	ccacccggac	ctggccgcca	ggaacgtcct	1980
ggtgacggag	gacaacgtga	tgaagatcgc	ggacttcgg	cttgctcgag	acatccacca	2040
catcgactac	tataaaaaga	caaccaacgg	ccgactgccc	gtcaaattgga	tggccacccga	2100
ggccttgttt	gaccggatct	acacccacca	gagcgacgt	ttgtctttg	gggtgctct	2160
ctggaaatc	ttcactctgg	gcccgtcccc	ataccctgg	gtccccgtgg	aggagcttt	2220
caagctgctg	aaggagggtc	atcgatgatg	caagccccagt	aactgcacca	acgagctcta	2280
catgatgatg	agagattgt	ggcacgcggt	ccctctcag	agacccacct	tcaagcagct	2340
ggtggaagac	ctggaccgca	tctggccctt	gacctccaa	caggagtacc	tggacctgtc	2400
aatgcccctg	gaccaatact	cccccagtt	ccccgacacc	cgcagctcca	cctgctctc	2460
cggggaggat	tccgtctttt	ctcacgagcc	cttgcccgag	gaaccctgca	tgccccgaca	2520

-continued

cccgccccag ctggccaacg gcggactcaa acggcgctga ctggcccca caccggcac	2580
cccttcccg actccatcct caacgccttg cccttcctcc cgctggactc gctgcctccc	2640
ctgcgtctg ctggccggcc tccctgaggc ccgcacccccc gagetcccct ccttcctcc	2700
tcccagctg acagaggagc agggaaagccg gtcccttgcgt acggctacta cgtggctgc	2760
ccaacgctgg accaagaccc cctccctgcc gcctggaggg ttgggcagtg agggctgagc	2820
cgcctcgag cgagagccga ctgagcttcc ctgcattggg tttgcgtact ctgcgcagcc	2880
catggcccggt gttctgtggc agatcctcgcc gcctggaggg gagttgggtg taggggtgg	2940
cagcgcggcg gcctccgcag ggcacccctgc ttccagacgg atagtgccag tggttattg	3000
atccgaaac taatttgcct tgctgaccaa atacctggta cccgagggtg gggacgcaga	3060
ggccggggagc cggcgccgtg gccctggggc ccagccccga agcaggggct ctgtacatag	3120
ctacgaagaa aacacaaagt gtataaatct gagtatatat ttacatgtct ttttaaagg	3180
gtcggttacca gagatttacc cattggtaa gatgctcctg gtgggtggg ggcacgtt	3240
gctatatatt aaaaacaaag aaaaagaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa	3300
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa	3360
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa	3400

<210> SEQ ID NO 15

<211> LENGTH: 846

<212> TYPE: PRT

<213> ORGANISM: Bos taurus

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (453) ... (453)

<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 15

Met Gly Leu Thr Ser Thr Trp Arg Tyr Gly Arg Gly Gln Gly Ile Gly			
1	5	10	15

Thr Val Thr Met Val Ser Trp Gly Arg Phe Leu Cys Leu Val Val Val			
20	25	30	

Thr Met Ala Thr Leu Ser Leu Ala Arg Pro Ser Phe Asn Leu Val Asp			
35	40	45	

Asp Thr Thr Val Glu Pro Glu Glu Pro Pro Thr Lys Tyr Gln Ile Ser			
50	55	60	

Gln Pro Glu Val Tyr Val Ala Ala Pro Arg Glu Ser Leu Glu Leu Arg			
65	70	75	80

Cys Leu Leu Arg Asp Ala Ala Met Ile Ser Trp Thr Lys Asp Gly Val			
85	90	95	

His Leu Gly Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln			
100	105	110	

Ile Lys Gly Ala Thr Pro Arg Asp Ser Gly Leu Tyr Ala Cys Thr Ala			
115	120	125	

Ala Arg Asn Val Asp Ser Glu Thr Val Tyr Phe Met Val Asn Val Thr			
130	135	140	

Asp Ala Ile Ser Ser Gly Asp Asp Glu Asp Asp Ala Asp Gly Ser Glu			
145	150	155	160

Asp Phe Val Ser Glu Asn Ser Asn Ser Lys Arg Ala Pro Tyr Trp Thr			
165	170	175	

Asn Thr Glu Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn			
180	185	190	

-continued

Thr Val Lys Phe Arg Cys Pro Ala Gly Gly Asn Pro Thr Pro Thr Met
 195 200 205
 Arg Trp Leu Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly
 210 215 220
 Gly Tyr Lys Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val
 225 230 235 240
 Val Pro Ser Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Asp Tyr
 245 250 255
 Gly Ser Ile Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro
 260 265 270
 His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Thr Val
 275 280 285
 Val Gly Gly Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln
 290 295 300
 Pro His Ile Gln Trp Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr
 305 310 315 320
 Gly Pro Asp Gly Leu Pro Tyr Leu Lys Val Leu Lys His Ser Gly Ile
 325 330 335
 Asn Ser Ser Asn Ala Glu Val Leu Ala Leu Phe Asn Val Thr Glu Ala
 340 345 350
 Asp Ala Gly Glu Tyr Ile Cys Lys Val Ser Asn Tyr Ile Gly Gln Ala
 355 360 365
 Asn Gln Ser Ala Trp Leu Thr Val Leu Pro Lys Gln Gln Ala Pro Val
 370 375 380
 Arg Glu Lys Glu Ile Pro Ala Ser Pro Asp Tyr Leu Glu Ile Ala Ile
 385 390 395 400
 Tyr Cys Ile Gly Val Phe Phe Ile Ala Cys Met Val Val Thr Val Ile
 405 410 415
 Leu Cys Arg Met Arg Asn Thr Thr Lys Lys Pro Asp Phe Ser Ser Gln
 420 425 430
 Pro Ala Val His Lys Leu Thr Lys Arg Ile Pro Leu Arg Arg Gln Val
 435 440 445
 Thr Glu Ser Arg Xaa Arg Val Ser Ala Glu Ser Ser Ser Met Asn
 450 455 460
 Ser Asn Thr Pro Leu Val Arg Ile Thr Thr Arg Leu Ser Ser Thr Ala
 465 470 475 480
 Asp Thr Pro Met Leu Ala Gly Val Ser Glu Tyr Glu Leu Pro Glu Asp
 485 490 495
 Pro Lys Trp Glu Phe Pro Arg Asp Lys Leu Thr Leu Gly Lys Pro Leu
 500 505 510
 Gly Glu Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Val Gly Ile
 515 520 525
 Asp Lys Glu Lys Pro Lys Glu Ala Val Thr Val Ala Val Lys Met Leu
 530 535 540
 Lys Asp Asp Ala Thr Glu Lys Asp Leu Ser Asp Leu Val Ser Glu Met
 545 550 555 560
 Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu
 565 570 575
 Gly Ala Cys Thr Gln Asp Gly Pro Leu Tyr Val Ile Val Glu Tyr Ala
 580 585 590
 Ser Lys Gly Asn Leu Arg Glu Tyr Leu Arg Ala Arg Arg Pro Pro Gly
 595 600 605
 Met Glu Tyr Ser Tyr Asp Ile Asn Arg Val Pro Glu Glu Gln Met Ala

US 9,226,960 B2

79

80

-continued

610	615	620
Phe Lys Asp Leu Val Ser Cys Thr Tyr Gln Leu Ala Arg Gly Met Glu		
625	630	635
Tyr Leu Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn		
645	650	655
Val Leu Val Thr Glu Asn Asn Val Met Lys Ile Ala Asp Phe Gly Leu		
660	665	670
Ala Arg Asp Ile Asn Asn Ile Asp Tyr Tyr Lys Lys Thr Thr Asn Gly		
675	680	685
Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val		
690	695	700
Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Met Trp Glu		
705	710	715
Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu		
725	730	735
Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn		
740	745	750
Cys Thr Asn Glu Leu Tyr Met Met Arg Asp Cys Trp His Ala Val		
755	760	765
Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg		
770	775	780
Ile Leu Thr Leu Thr Thr Asn Glu Glu Tyr Leu Asp Leu Ser Gln Leu		
785	790	795
Leu Glu Gln Tyr Ser Pro Ser Tyr Pro Asp Thr Arg Ser Ser Cys Ser		
805	810	815
Ser Gly Asp Asp Ser Val Phe Ser Pro Asp Pro Met Pro Tyr Glu Pro		
820	825	830
Cys Leu Pro Gln Tyr Pro His Arg Asn Gly Ser Val Lys Thr		
835	840	845

<210> SEQ_ID NO 16

<211> LENGTH: 4302

<212> TYPE: DNA

<213> ORGANISM: Bos taurus

<400> SEQUENCE: 16

```

ttttttttt tgcggggagt tggtcgtttg ctccatcccc acccacgctg ggcgcgggga      60
cagacccat cgccggggat cgttgccatt caagaggctg cagcagcagc agcagcagca     120
ggggcaaggc cagcgagcgg ccggccgcgc accttggttc ctgagcccc acggcgctga     180
aggcattgct gcaggcagtc catgctcgta gaggaagggt gcagatggga ttaacgtcca     240
catggagata tggaaagagga caggggatcg gcactgtaaac catggtcagc tggggtcgct    300
tccctctgcct ggttgtggtc accatggcaa cttgtccct ggcccgcccc tccctcaatt    360
tagttgacga taccacggtt gagccggaaag agccaccaaac caaatccaa atctccaaac    420
cagaagttt cgtggctgcg cccggggagt cgctagagt ggcgtgcctg ttgcgagatg    480
ccgcccattat cagttggact aaggatgggg tacacttggg gcccaacaat aggacagtgc    540
ttattggggta gtatttgcaat ataaaagggtt ccacgcctag agactccggc ctctatgctt   600
gtactgctgc taggaacgta gacagtgaga ctgtctactt catggtaat gtcacagatg    660
ccatctcattt cggagatgtat gaggacgacg cagatggctc ggaggattt gtcagtgaga    720
acagtaacag caagagagca ccatactgga ccaacacaga aaagatggaa aaacggctgc    780
acgcggtcccc acgagccaac actgtcaagt tccgctgtcc agctgggggg aatccaacac    840

```

-continued

caaccatgag gtggctgaaa aacgggaagg aatthaagca ggagcatcgc attggaggct	900
ataaggtacg aaaccagcat tggagcccta ttatggaaag tgggtcccg tctgacaaag	960
gaaattatac ctgcgtggtg gagaacgatt acgggtccat caatcatacg taccacctt	1020
acgttgttga gcgatcacca caccggccca tcctccaagg cggtgtgccg gcaaatacgct	1080
ccactgtggt tggaggcgat gtggagttt tctgcaaagt gtacagcgat gcccagcccc	1140
atatccatgt gatcaaacac gtggaaaaga acggcagtaa atatggccc gacgggtcgc	1200
cctatctcaa ggttctgaag cactcgggta taaatagttt caatcgaaaa gtgtggctc	1260
tgttcaatgt gacggggcg gatgtggcg agtatattttt taagggtctcc aattatata	1320
ggcaggccaa ccagtctgcc tggctcaactg tcctgccaaa acagcaagct cctgtaaag	1380
aaaaggagat ccacgttcc ccacactacc tggaaatagc catttactgc ataggggtgt	1440
tcttcatcgc ctgcattggtg gtgacggtca tcttggcccg gatgagggaa acgaccaaga	1500
agccggactt cagcagccag cccgggtgtgc acaagctgac caagcgcaccc cccctgcgg	1560
gacaggttaac agaaagttaga taaagagttt ctgtgtggc cagctctcc atgaactcca	1620
ataccccggtt ggtgaggatt acaactcgcc tctttcaac tgcagacacc cccatgtgg	1680
cggggggtctc caggtacgag ctgcagaag atcccaatgg gtagttcca agagataagc	1740
tgacgctggg caaacccctg ggagaagggtt gctttggca agtgggtcatg gctgaagcag	1800
tgggaattga caaggagaag cccaaaggaa cagtcactgt ggccgtgaag atgttgaag	1860
atgtgtccac tgagaaagac ctttctgatc tgggtgtccg gatggagatg atgaagatga	1920
ttggaaaca caaaaatatac ataaatctcc ttggagectg tactcaggat gggccgtct	1980
atgtcatcg tgaatacgcc tctaaaggca accttcgggaa atacctgcgc gccccggaggc	2040
cacccgggat ggagtattcc tacgacatca accgcgttcc cgaggagcag atggcctca	2100
aggacctggt gtcgtgtacc taccagctgg cccggggcat ggagtactg gtttccaga	2160
aatgcattca tcgagattt gctgccagaa atgttttgtt aacagaaaac aacgtgtatga	2220
aaatagctga ctggactg gccagagata tcaacaatag actattac aaaaagacca	2280
caaatggccg acttcgggtc aagtggatgg ctcccgaaac cttttcgac agagtgtaca	2340
cccatcagag cgtgtctgg tccttcgggg tgttaatgtt ggagatctc acgttaggg	2400
gttcgcctca cccaggattt cccgtggagg aactttttaa gctgttaag gaaggacata	2460
ggatggacaa gccagaaac tgcaccaacg aactgtatata gatgtgtgaga gactgtggc	2520
atgcgttacc ctcacagaga cccaccttca agcagtttgtt agaagacttg gatcgaattc	2580
tcacactcac aaccaatggaa gataacttgg acctcgtca gtttcttgcgaa caatattcac	2640
ctagttaccc tgacacaagg agtcttgc ttcggggata tgattctgtt ttctctccgg	2700
accccatgcc ttacgaaccc tgccttcctc agtattccaca tagaaacggc agtgttaaaa	2760
catgaatggg cctgtccccca tggccaaa cagggtggca tcaggaactt agctgtactg	2820
agcagggggg gccttgcctc caggagcctg ttggcttggc ttgtatataat ggatcagagg	2880
agtaaatattt tggaaaagtgt atcggcacac gtgtaaagaa ttatccagt tggagacttg	2940
taatcttac caggagaaca agaagggtgtt gggggcaatg gattgcacatg ggccgcac	3000
tgcttgcac ccaccgtggg tactggctgt ggaccagccg gacttgaggc aaacaccgt	3060
tctgcctgcc ttgtgaattt tgcataattt ggagaaaata tatgtcagcg cacactata	3120
gagcacaattt gcagttatata ggtgtggat gtatgtaaat atattcaat tatgtataaa	3180

-continued

tatataattat atatttacaa ggaatttattt tttgtattga ttttaaatgg atgtcccagc	3240
gcaccttagaa aattggcttc tctctctttt tttaaaaat agctatttgc taaatgctgt	3300
ttcttacata gaatttctta atttcaccc agcagaggtg gaaaagtact tttgtttca	3360
ggaaaaatg atatgacatt aatttattaa tgaattggta atatacaaaa caatcgttt	3420
tttgtttttt ttttgtaat ttaagtggca tttctatgca ggcagcacac cagactagtt	3480
aatctcttc ttaacttaa ctatgttca gatcctctga aaagagaaat atttacaaaa	3540
tgtgactaat ttggggaaag tgaagtttg gtttatttg atttcagctc tgctgtcaga	3600
tgattggct ttaaccacct aactgcccgt atgaaagagc ccattgtatga gaagggtgt	3660
tgtcttgggt cagcttggc attggggcca taaaccccttc actgggcttc ccaagacaaa	3720
cggtaccaggc gttccctaa aaagatgcct taatctgttcc tcacaaggag gaactctcat	3780
c gagatgcta aaagaatgtt ctgtccagcc gctggccttc tgcccccttc cccgccaagt	3840
tgcacattga tcagatcagc ctgcatttcc tttggcgaat cttcatcaca gttccagat	3900
ttactggcaa cagagaagtc tcttagaattt ttcacgcccgt gtcggagaaa atggaaacac	3960
tgagttgttc tgctgtatgt ttggggatc cttccatctt tttaaggat cgcttccgcc	4020
tcctctggca ggatctcacc gaaagatccc gcccattatgcc aatgtcatgt tactgcatg	4080
gtgttcgttt tttatgtaaacg tggtgtgtt tgcttcaaa acaccttctc actctgctct	4140
ggctgtgcaaa catgaatgctg gatgacactg atttttaacg tgttatgaaa ttggagaaaag	4200
tatataataa aacctgttaa ttttataact gacaataaaa atgtttctac agatattaat	4260
gttaacaaga caaaataaat gtcatgcggc ttatTTTTT aa	4302

<210> SEQ_ID NO 17

<211> LENGTH: 802

<212> TYPE: PRT

<213> ORGANISM: Bos taurus

<400> SEQUENCE: 17

Met	Gly	Ala	Pro	Ala	Arg	Ala	Leu	Ala	Phe	Cys	Val	Ala	Val	Ala	Val
1							5				10			15	

Met	Thr	Gly	Ala	Ala	Leu	Gly	Ser	Pro	Gly	Val	Glu	Pro	Arg	Val	Ala
							20			25			30		

Arg	Arg	Ala	Ala	Glu	Val	Pro	Gly	Pro	Glu	Pro	Ser	Pro	Gln	Glu	Arg
							35			40			45		

Ala	Phe	Gly	Ser	Gly	Asp	Thr	Val	Glu	Leu	Ser	Cys	Arg	Leu	Pro	Ala
							50			55			60		

Gly	Val	Pro	Thr	Glu	Pro	Thr	Val	Trp	Val	Lys	Asp	Gly	Val	Gly	Leu
							65			70			75		80

Ala	Pro	Ser	Asp	Arg	Val	Leu	Val	Gly	Pro	Gln	Arg	Leu	Gln	Val	Leu
							85			90			95		

Asn	Ala	Ser	His	Glu	Asp	Ala	Gly	Ala	Tyr	Ser	Cys	Arg	Gln	Arg	Leu
							100			105			110		

Ser	Gln	Arg	Leu	Leu	Cys	Leu	Phe	Ser	Val	Arg	Val	Thr	Asp	Ala	Pro
							115			120			125		

Ser	Ser	Gly	Asp	Asp	Glu	Gly	Gly	Asp	Asp	Glu	Ala	Glu	Asp	Thr	Ala
							130			135			140		

Gly	Ala	Pro	Tyr	Trp	Thr	Arg	Pro	Glu	Arg	Met	Asp	Lys	Lys	Leu	Leu
							145			150			155		160

Ala	Val	Pro	Ala	Ala	Asn	Thr	Val	Arg	Phe	Arg	Cys	Pro	Ala	Ala	Gly
							165			170			175		

-continued

Asn Pro Thr Pro Ser Ile Thr Trp Leu Lys Asn Gly Lys Glu Phe Arg
 180 185 190
 Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg Gln Gln Gln Trp Ser
 195 200 205
 Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn Tyr Thr Cys
 210 215 220
 Val Val Glu Asn Lys Phe Gly Arg Ile Gln Gln Thr Tyr Thr Leu Asp
 225 230 235 240
 Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro
 245 250 255
 Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys
 260 265 270
 Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Glu
 275 280 285
 Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val
 290 295 300
 Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu Leu Glu Val Leu
 305 310 315 320
 Ser Leu Arg Asn Val Thr Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu
 325 330 335
 Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala Trp Leu Val Val
 340 345 350
 Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Gly Glu Ala Gly Gly Val
 355 360 365
 Phe Ala Gly Val Leu Ser Tyr Gly Leu Gly Phe Leu Leu Phe Ile Leu
 370 375 380
 Ala Val Ala Ala Val Thr Leu Tyr Arg Leu Arg Ser Pro Pro Lys Lys
 385 390 395 400
 Gly Leu Gly Ser Pro Ala Val His Lys Val Ser Arg Phe Pro Leu Lys
 405 410 415
 Arg Gln Val Ser Leu Glu Ser Ser Ser Met Ser Ser Asn Thr Pro
 420 425 430
 Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly Pro Thr Leu Ala
 435 440 445
 Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys Trp Glu Leu Ser
 450 455 460
 Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly
 465 470 475 480
 Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp Arg Ala Ala
 485 490 495
 Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Asp
 500 505 510
 Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile
 515 520 525
 Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Gly
 530 535 540
 Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys Gly Asn Leu Arg
 545 550 555 560
 Glu Tyr Leu Arg Ala Arg Arg Pro Pro Gly Thr Asp Tyr Ser Phe Asp
 565 570 575
 Thr Cys Arg Leu Pro Glu Glu Gln Leu Thr Phe Lys Asp Leu Val Ser
 580 585 590
 Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys

-continued

595	600	605
Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val	Leu Val Thr Glu Asp	
610	615	620
Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Val His Asn		
625	630	635
640		
Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp		
645	650	655
Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp		
660	665	670
Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly		
675	680	685
Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys		
690	695	700
Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr His Asp Leu Tyr		
705	710	715
720		
Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr		
725	730	735
Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu Thr Val Thr Ser		
740	745	750
Thr Asp Glu Tyr Leu Asp Leu Ser Val Pro Phe Glu Gln Tyr Ser Pro		
755	760	765
Gly Gly Gln Asp Thr Pro Ser Ser Gly Ser Ser Gly Asp Asp Ser Val		
770	775	780
785	790	795
800		
Arg Thr		

```
<210> SEQ ID NO 18
<211> LENGTH: 2562
<212> TYPE: DNA
<213> ORGANISM: Bos tauru
```

<400> SEQUENCE: 18
ggccatgggg ggcagcatgc tggegcgcgc cgcctgagga cgccgcaccc cccggccccg 60
cgatggcgc cccggctgc gcctcgct ttgcgtggc agtggcggtc atgaccggcg 120
ccgcccctcggt gtccccgggc gtggagcccc gcgtcgccgc gagaggccca gaggtcccg 180
gccccgagcc cagccccgagc gagcggggct ttggcagcggt ggacaccgtg gagctgagct 240
ggcgcttgcc ggcggggggtg cccacagagc ccaccgtctg ggtgaaggac ggcgtggcc 300
tggcgccctc ggaccgcgtc ctgggtgggc cgcagggct acagggtgtc aacgcctccc 360
acgaggacgc cggagccctac agctgccgcc agcgcccttc ccagcggtctg ctgtccctct 420
tcagcggtgcg cgtgacagat gctccgtctt caggggatga cgagggtggg gacgacgagg 480
ccgaggacac agctggggcc ccttaacttggc cgccgcctga cgccatggac aagaagctgc 540
tagcggtgca ggccgcacaac acggttcgat tccgctgccc agctgtgtggc aaccacacgc 600
catccatcac ctggctgaag aacggcaagg agttccgggg cgagcacccgc atcgggggaa 660
tcaaactgca gcagcagcag tggagcctgg tcatggagag cgtgggtccc tcggaccgcg 720
gcaactacac gtgcgtcgat gagaacaagt tcggcagaat ccagcagacc tacaccctgg 780
acgtgctggc ggcgtctccg caccggccca tcctacaggc cgggctgccc gctaaccaga 840
cagccgtgtt gggcagcgat gtggagttcc actgcaaggat ctacaggcgc gcccagcccc 900
acatccaatq qctcaaqcgc qttqqqqqta acqqcaqcaaa qqtqqqqqccc qacqqcqcq 960

-continued

ctacgtc acgtgctcaag acggccggcg ctaacaccac cgacaaggag cttagggttc
tatccttgcg caatgtcacc tttgaggacg cgggggagta cacatgtctg gcgggcaatt
ctatcggtt ttccccatcac tctgcgtggc tgggtgtgtt gccaatgtgag gaggagctgg
tggaagcccg tgaggotggc ggtgtgttcg cgggtgttct cagctacggg ctgggcttcc
tcctcttcat cctggccgtg gcccgcgtt cgccttacccg cctgaggagc cccccctaaga
agggcctggg ctgcgcgcgcg gtgcacaagg tctccgcgtt cccgctcaag cgacaggtgt
ccttggagtc cagctcatcc atgagctcca acacaccgct ggtacgcatt gccccgtgt
catcgccgca gggccccacc ctggccaacg tctctgagct cgagctgccc gcccggccca
agtggggagct gtcccccggcc cggctgaccc tgggcaagcc tcttggggag ggctgcttcg
gcacgggtgtt catggcagag gccattggca tgcacaaggaa ccgagctgcc aagectgtca
cggtggccgt gaagatgtct aaagatgtacg ccacggataa ggacttatacg gacctgggt
ccgagatggaa gatgtatggaa atgatcgaa aacacaagaa cattatcaac ctgtcttaggg
cctgcacgca gggccggccccc ctgtacgtgc tgggtggagta cgccggcaag ggcaacactgc
gggaataacct gcgggcacgg cggccccccgg gcactgacta ctcccttcgac acctggccgc
tgcccgagga gcagctcacc ttcaaagacc tgggtgttctg cgccttaccag gtggccgggg
gcattggatgtt cctggcttcg cagaagtgtca tccacaggaa cctggccggcc cgcaacgtgc
tgggtactga ggacaacgtg atgaaaatcg cgcacttcgg cctggctcgt gacgtgcaca
acctcgacta ctacaaaaag accacaaaacg gcccgcgtt cgtgaagtgg atggcaccgg
aggccttgtt tgaccgcgtc tacacccacc aaagtgtacgt ctgggttctt ggggttctgc
tctggggatgtt cttcacgcgtg gggggctcgc cgttaccccg catccccgtt gaggagctct
tcaagctgtgtt gaaggaagtc caccgcgtt acaagccggc caactgcacg catgacactgt
acatgtatcat ggcgcgttgc tggcacggcg cgccttcgtt gaggccacc ttcaagcagg
tgggtggagga cctggccgtt gtgcgttccgt tgacgttccac cgacgttac ctggccctgt
cggtggccctt cgacgttac tgcacggcgcc gtcaggacac ccccaatgtcc ggcttctegg
ggggacgttcc cgtgttccgtt caccgttccgt tgcccccggc cccatccggc agcggagggt
cgccggacgtt aagggttccgtt gcccggccgtt cgcgttccatc tcaatgttgc aacagacccc
agcccccattt gctgcgttgc ggcgttccatc atcccttggt cc
1020
1080
1140
1200
1260
1320
1380
1440
1500
1560
1620
1680
1740
1800
1860
1920
1980
2040
2100
2160
2220
2280
2340
2400
2460
2520
2582

<210> SEQ ID NO 19

<211> LENGTH: 800

<212> TYPE: PRT

<213> ORGANISM: Bos taurus

<400> SEQUENCE: 19

Met Arg Leu Leu Leu Val Leu Leu Gly Val Leu Leu Gly Ala Pro Gly
1 5 10 15

Ala Pro Ala Leu Ser Phe Glu Ala Ser Glu Glu Thr Glu Leu Glu Pro
20 25 30

Cys Leu Ala Pro Ser Pro Glu Gln Gln Glu Gln Glu Leu Thr Val Ala
35 40 45

Leu Gly Gln Pro Val Arg Leu Cys Cys Gly Arg Ala Glu Arg Ser Gly
50 55 60

His	Trp	Tyr	Lys	Glu	Gly	Ser	Arg	Leu	Thr	Pro	Ala	Gly	Arg	Val	Arg
65				70					75					80	

Gly Trp Arg Gly Arg Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala

US 9,226,960 B2

91**92**

-continued

85	90	95	
Gly Gln Tyr Leu Cys Leu Ser Arg Gly Ser Leu Leu Leu His Asn Val			
100	105	110	
Thr Leu Val Val Asp Asp Ser Met Thr Ser Ser Asn Gly Asp Glu Asp			
115	120	125	
Pro Lys Ile His Arg Gly Pro Leu Asn Gly His Val Tyr Pro Gln Gln			
130	135	140	
Ala Pro Tyr Trp Thr His Pro Gln Arg Met Glu Lys Lys Leu His Ala			
145	150	155	160
Val Pro Ala Gly Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly Asn			
165	170	175	
Pro Met Pro Thr Ile Arg Trp Leu Lys Asp Gly Gln Asp Phe His Gly			
180	185	190	
Glu His Arg Ile Gly Gly Ile Arg Leu Arg His Gln His Trp Ser Leu			
195	200	205	
Val Met Glu Ser Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys Leu			
210	215	220	
Val Glu Asn Ser Leu Gly Ser Ile Arg Tyr Ser Tyr Leu Leu Asp Val			
225	230	235	240
Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala			
245	250	255	
Asn Thr Thr Ala Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys Val			
260	265	270	
Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Ile Val Ile			
275	280	285	
Asn Gly Ser Ser Phe Gly Ala Asp Gly Phe Pro Tyr Val Gln Val Leu			
290	295	300	
Lys Thr Ala Asp Ile Asn Ser Ser Glu Val Glu Val Leu Tyr Leu Arg			
305	310	315	320
Asn Val Ser Ala Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn			
325	330	335	
Ser Ile Gly Leu Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro Glu			
340	345	350	
Glu Asp Leu Thr Trp Thr Ala Thr Ala Pro Glu Gly Arg Tyr Thr Asp			
355	360	365	
Ile Ile Leu Tyr Ser Ser Gly Ser Leu Ala Leu Ile Val Phe Leu Leu			
370	375	380	
Leu Val Gly Leu Tyr Arg Arg Gln Thr Leu Leu Thr Arg His His Arg			
385	390	395	400
Gln Pro Ala Thr Val Gln Lys Leu Ser Arg Phe Pro Leu Ala Arg Gln			
405	410	415	
Phe Ser Leu Glu Ser Gly Ser Ser Ala Lys Ser Ser Leu Ser Leu Val			
420	425	430	
Arg Gly Val Arg Leu Ser Ser Ser Gly Pro Pro Leu Leu Ala Gly Leu			
435	440	445	
Val Ser Leu Asp Leu Pro Leu Asp Pro Leu Trp Glu Phe Pro Arg Asp			
450	455	460	
Arg Leu Val Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val			
465	470	475	480
Val Cys Ala Glu Ala Phe Gly Met Asp Pro Thr Arg Pro Asp Gln Ala			
485	490	495	
Ser Thr Val Ala Val Lys Met Leu Lys Asp Asn Ala Ser Asp Lys Asp			
500	505	510	

-continued

Leu Ala Asp Leu Val Ser Glu Met Glu Val Met Lys Leu Ile Gly Arg
 515 520 525
 His Lys Asn Ile Ile Asn Leu Leu Gly Val Cys Thr Gln Glu Gly Pro
 530 535 540
 Leu Tyr Val Ile Val Glu Cys Ala Ala Lys Gly Asn Leu Arg Glu Phe
 545 550 555 560
 Leu Arg Ala Arg Arg Pro Pro Gly Pro Asp Leu Ser Pro Asp Gly Pro
 565 570 575
 Arg Ser Ser Glu Gly Pro Leu Ser Phe Pro Ala Leu Val Ser Cys Ala
 580 585 590
 Tyr Gln Val Ala Arg Gly Met Gln Tyr Leu Glu Ser Arg Lys Cys Ile
 595 600 605
 His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val
 610 615 620
 Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Gly Ile His His Ile Asp
 625 630 635 640
 Tyr Tyr Lys Lys Thr Ser Asn Gly Arg Leu Pro Val Lys Trp Met Ala
 645 650 655
 Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp
 660 665 670
 Ser Phe Gly Ile Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro
 675 680 685
 Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Ser Leu Leu Arg Glu Gly
 690 695 700
 His Arg Met Asp Arg Pro Pro His Cys Pro Pro Glu Leu Tyr Gly Leu
 705 710 715 720
 Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe Lys
 725 730 735
 Gln Leu Val Glu Ala Leu Asp Lys Val Leu Leu Ala Val Ser Glu Glu
 740 745 750
 Tyr Leu Asp Leu Arg Leu Thr Phe Gly Pro Tyr Ser Pro Ala Gly Gly
 755 760 765
 Asp Ala Ser Ser Thr Cys Ser Ser Ser Asp Ser Val Phe Ser His Asp
 770 775 780
 Pro Leu Pro Leu Arg Pro Ser Ser Phe Ser Phe Pro Gly Val Gln Thr
 785 790 795 800

<210> SEQ ID NO 20

<211> LENGTH: 3139

<212> TYPE: DNA

<213> ORGANISM: Bos taurus

<400> SEQUENCE: 20

```

atccctggct ctgcggccgg gggctgcgca actccccagc agtcttctgt ctccgctggg      60
cgtgggggtc cgggctggcg ggagctgaga gcgaggccgc ggaggaccga gaaaggcagt     120
cataggaggc ccagcctggg tcctcgagag cggcaggaag gagatgcggc tgctgttgt     180
cctcctgggg gtccctgtgg gggcacctgg ggccctcagct ttgtcccttg aggccctctga   240
ggaaacggag ctggagccct gcctggcccc cagcccgag cagcaagagc aggagttgac     300
ggtgccctt gggcagcctg tgccggttatg ctgcggccgg gctgagcgcga gtggccactg   360
gtacaaggag ggcagtcgcc tgacacctgc tggccgggtta cgaggctgga gaggccgctt   420
ggagattgcc agttcctac ccgaggatgc tggccagtagt acatgcctat cacgaggctc   480

```

-continued

cttgcttcgt cacaacgtca ccttggttgt ggacgactcc atgaccccca gcaatggcga	540
cgaggacccc aagatccaca gggggccctt gaatgggcac gtttaccccc agcaagcacc	600
ctactggacg caccccccagc gcatggagaa gaaaactgcat gctgtgcctg ccggaaacac	660
cgtcaagttc cgctgtccag ctgcaggcaa cccatgcc accatecgct ggctcaagga	720
tggacaggac ttccacgggg agcatcgcat tggaggcatt cggctgcgcc accagcactg	780
gagcctggtg atggaaagcg tggtgccctc tgaccgtggc acttacacct gcctegtgga	840
gaattcttg ggcagcattc gctatagcta cctgctggac gtgctggagc ggtccccgca	900
ccggcccatc cttcaggcag ggctcccagc caacaccacg gctgtgggg gcagtgcgt	960
ggaactgctc tgcaagggtgt acagcgacgc ccagccccac atccagtggc tgaagcacat	1020
cgtcatcaac ggcagcagct tcggtgccga cggcttcccc tatgtgcaag tcttaagac	1080
agcggacatc aatacgctcg aggtggaggt cttgtacctt cggaaatgtat ctgctgagga	1140
tgcaggcag tacacctgcc tggcgggcaa ctccatcgcc ctttcttacc agtccggctg	1200
gtcacaagggtg ctggccaggagg aggatctcactc gtggacacgc acagcccccg aaggcaggta	1260
cacggacatc atccctgtact cgtagggctc tctggctttg atcgtgttcc tgctgctgg	1320
cgggctatat cgcaggcaga cgctccctac ccgacaccac cgacagcccc ccaccgtgca	1380
gaagttgtct cgcttcctc tggcccgaca gttctcgctg gagtcaggct cctcagccaa	1440
gtcaaggttg tccctgggtgc ggggtgtccg tctctccctc agcggcccccc ctttgctcgc	1500
tggcctcggt agtctcgacc tggcttctga cccactgtgg gagttcccc gggacaggct	1560
ggtgctggga aagccccctgg gcgaggcgtg ctttggcag gtgggtgtgcg cagaggcctt	1620
cggcatggac cccaccggc cagaccaagc cagcaccgtg gctgtcaaga tgcttaagga	1680
caacgcctcc gacaaggact tggcagacact ggtctctgag atggaggtga tgaagctgat	1740
tggccgacac aagaacatta tcaacctgct ggggtgtctgc acccaggaag ggcccttgt	1800
cgtgatcggtg agtgtgtctg ccaaggggca cctgcggggat tccctgcggg cccgcggccc	1860
cccaggccct gacctcagcc ctgacgggcc tcggagcagc gagggggccgc tctccccc	1920
tgcctcggtc tccctgcgcct accaggtggc cggggcatg cagtagctgg agtcccgaa	1980
gtgcacccac cgggacctgg ctgcccgc aa tgcgtgtgg accgaggaca atgtgtatgaa	2040
gattgcacac ttcgggctgg cccgtggcat ccaccacatt gactactaca agaaaaactag	2100
caacggccgc ctgcctgtca agtggatggc accagaggcc ttgtttgaca gagtctacac	2160
acaccagagt gatgtgtggt cgtttggaat cctgctgtgg gagatctca ccctcggggg	2220
ctccccatac cctggcatcc ccgtggagga gctgttctcg ctgctacgag aggggcac	2280
gatggacccgg ccccccacact gccccccaga gctatacggg ctgatgcgcg agtgcgtggca	2340
cgcacccaccc tctcagaggc ccacttcaa gcaactggta gaggcactgg acaaggctt	2400
gtggccgtc tctgaggagt acctcgacact ccgcctaaacc ttggacccct actccctgc	2460
cgccggggac gccagcagca cctgctccctc tagcgactct gtctcagcc acgaccct	2520
accactgagg cccagctccct tctccctccc tgggggtgcag acgtgagcag aggccacaggc	2580
tgtatgggca gggtcagctg ccagccttgg gcctcctggc tcaactgaaa ccaggtggca	2640
ctcgcttgc gcaaaaaacccag gcctgcaccc aagggtacta tcccgatct ctggttctgt	2700
ttggggagg tctgcttgc gtcctgggtt ccctgtctc gagactctt tctctggcct	2760
ctgggtctca agccagagtt caatcccagc ctcaaggccc tggctttgg agtgcgtggcc	2820
ccagtttctt aatggtttgt taagggtctg ctggacttc tggcccttgg tagaagtctt	2880

-continued

tgttccaggg	ctttggttgg	acctggctgc	agggctgtct	taaacctccc	cgcttcccc	2940
taccaagaga	ggtcttagac	ctctgaaccc	caactcccca	ggcctccct	gcctccctct	3000
gtgtgtgtc	ccagcatctt	gatggaaagga	gcgcgtgtgc	ccacccatc	cccacaccgc	3060
cccgtgtgg	ctgagaggct	gggagcctac	caaaacacag	aagcaaatga	cctttataaa	3120
attatttttt	tgaaatgaa					3139

<210> SEQ ID NO 21

<211> LENGTH: 114

<212> TYPE: PRT

<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 21

Met	Ser	Leu	Ile	Phe	Phe	Thr	Leu	Tyr	Ile	Val	Ile	Phe	Ser	Leu	Leu
1				5			10				15				
Leu	Ile	Val	Lys	Leu	Gln	Leu	Gln	Ala	Glu	Glu	Arg	Gly	Val	Val	Ser
		20				25					30				
Ile	Lys	Gly	Val	Cys	Ala	Asn	Arg	Tyr	Leu	Ala	Met	Lys	Glu	Asp	Gly
	35				40						45				
Arg	Leu	Leu	Ala	Ser	Lys	Cys	Val	Thr	Asp	Glu	Cys	Phe	Phe	Phe	Glu
	50				55						60				
Arg	Leu	Glu	Ser	Asn	Asn	Tyr	Asn	Thr	Tyr	Arg	Ser	Arg	Lys	Tyr	Ser
	65					70			75			80			
Ser	Trp	Tyr	Val	Ala	Leu	Lys	Arg	Thr	Gly	Gln	Tyr	Lys	Leu	Gly	Pro
		85				90					95				
Lys	Thr	Gly	Pro	Gly	Gln	Lys	Ala	Ile	Leu	Phe	Leu	Pro	Met	Ser	Ala
	100					105					110				
Lys	Ser														

<210> SEQ ID NO 22

<211> LENGTH: 345

<212> TYPE: DNA

<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 22

atgtcttta	tcttcattac	cctgtatatt	gtatTTTTT	cTTATTACT	tATAGTCaaa	60
ctacaacttc	aaggcagaaga	gagagggggtt	gtgtctatca	aaggagtgtg	tgcaaaccgt	120
tatcttgcta	tgaaggaaga	tggagattta	ctggcttcta	aatgtgttac	agacgagtgt	180
ttcttttttg	aacgactgga	atctaataac	tacaataactt	accggcggag	gaaataactcc	240
agttggatag	tggcactgaa	acgaacgggg	cagtataaac	ttggacccaa	aacaggacct	300
gggcagaaag	ctatactttt	tcttccaatg	tctgctaaaga	gctgaa		345

<210> SEQ ID NO 23

<211> LENGTH: 818

<212> TYPE: PRT

<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 23

Met	Cys	Ser	Trp	Lys	Cys	Leu	Leu	Phe	Trp	Ala	Val	Leu	Val	Thr	Ala
1				5			10				15				
Thr	Leu	Cys	Thr	Ala	Arg	Pro	Ala	Pro	Thr	Ser	Pro	Glu	Gln	Ala	Gln
		20			25						30				
Pro	Trp	Gly	Ala	Pro	Val	Glu	Val	Glu	Ser	Phe	Leu	Val	His	Pro	Gly
		35			40						45				

US 9,226,960 B2

99**100**

-continued

Asp	Leu	Leu	Gln	Leu	Arg	Cys	Arg	Leu	Arg	Asp	Asp	Val	Gln	Ser	Ile
50						55						60			

Asn	Trp	Leu	Arg	Asp	Gly	Val	Gln	Leu	Val	Glu	Ser	Asn	Arg	Thr	Arg
65						70						80			

Ile	Thr	Gly	Glu	Glu	Val	Glu	Val	Arg	Asp	Ser	Val	Pro	Ser	Asp	Ser
85						90						95			

Gly	Leu	Tyr	Ala	Cys	Val	Thr	Ser	Ser	Pro	Ser	Gly	Ser	Asp	Thr	Thr
100						105					110				

Tyr	Phe	Ser	Val	Asn	Val	Ser	Asp	Ala	Leu	Pro	Ser	Ser	Glu	Asp	Asp
115						120					125				

Asp	Asp	Asp	Asp	Ser	Ser	Ser	Glu	Glu	Lys	Glu	Thr	Asp	Asn	Thr
130						135					140			

Lys	Pro	Asn	Pro	Val	Ala	Pro	Tyr	Trp	Thr	Ser	Pro	Glu	Lys	Met	Glu
145						150					155			160	

Lys	Lys	Leu	His	Ala	Val	Pro	Ala	Ala	Lys	Thr	Val	Lys	Phe	Lys	Cys
165						170					175				

Pro	Ser	Ser	Gly	Thr	Pro	Asn	Pro	Thr	Leu	Arg	Trp	Leu	Lys	Asn	Gly
180						185					190				

Lys	Glu	Phe	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val	Arg	Tyr
195						200					205				

Ala	Thr	Trp	Ser	Ile	Ile	Met	Asp	Ser	Val	Val	Pro	Ser	Asp	Lys	Gly
210						215					220				

Asn	Tyr	Thr	Cys	Val	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	Asn	His	Thr
225						230					235			240	

Tyr	Gln	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln
245						250					255				

Ala	Gly	Leu	Pro	Ala	Asn	Lys	Thr	Val	Ala	Leu	Gly	Ser	Asn	Val	Glu
260						265					270				

Phe	Met	Cys	Lys	Val	Tyr	Ser	Asp	Pro	Gln	Pro	His	Ile	Gln	Trp	Leu
275						280					285				

Lys	His	Ile	Glu	Val	Asn	Gly	Ser	Lys	Ile	Gly	Pro	Asp	Asn	Leu	Pro
290						295					300				

Tyr	Val	Gln	Ile	Leu	Lys	Thr	Ala	Gly	Val	Asn	Thr	Thr	Asp	Lys	Glu
305						310					315			320	

Met	Glu	Val	Leu	His	Leu	Arg	Asn	Val	Ser	Phe	Glu	Asp	Ala	Gly	Glu
325						330					335				

Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Leu	Ser	His	His	Ser	Ala
340						345					350				

Trp	Leu	Thr	Val	Leu	Glu	Ala	Leu	Glu	Arg	Pro	Ala	Val	Met	Thr
355						360					365			

Ser	Pro	Leu	Tyr	Leu	Glu	Ile	Ile	Tyr	Cys	Thr	Gly	Ala	Phe	Leu
370						375					380			

Ile	Ser	Cys	Met	Val	Gly	Ser	Val	Ile	Ile	Tyr	Lys	Met	Lys	Ser	Gly
385						390					395			400	

Thr	Lys	Lys	Ser	Asp	Phe	His	Ser	Gln	Met	Ala	Val	His	Lys	Leu	Ala
405						410					415				

Lys	Ser	Ile	Pro	Leu	Arg	Arg	Gln	Val	Ser	Ala	Asp	Ser	Ser	Ala	Ser
420						425					430				

Met	Asn	Ser	Gly	Val	Leu	Leu	Val	Arg	Pro	Ser	Arg	Leu	Ser	Ser	Ser
435						440					445				

Gly	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser	Glu	Tyr	Glu	Leu	Pro	Glu	Asp
450						455					460				

Pro Arg Trp Glu Leu Pro Arg Asp Arg Leu Val Leu Gly Lys Pro Leu

US 9,226,960 B2

101

-continued

465	470	475	480
-----	-----	-----	-----

Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	Val	Leu	Ala	Glu	Ala	Ile	Gly	Leu
							485		490					495	

Asp	Lys	Asp	Lys	Pro	Asn	Arg	Val	Thr	Lys	Val	Ala	Val	Lys	Met	Leu
							500		505				510		

Lys	Ser	Asp	Ala	Thr	Glu	Lys	Asp	Leu	Ser	Asp	Leu	Ile	Ser	Glu	Met
							515		520			525			

Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His	Lys	Asn	Ile	Ile	Asn	Leu	Leu
							530		535		540				

Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu	Tyr	Val	Ile	Val	Glu	Tyr	Ala
							545		550		555		560		

Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu	Gln	Ala	Arg	Arg	Pro	Pro	Gly
							565		570		575				

Leu	Glu	Tyr	Cys	Tyr	Asn	Pro	Ser	His	Asn	Pro	Glu	Gln	Leu	Ser
							580		585		590			

Ser	Lys	Asp	Leu	Val	Ser	Cys	Ala	Tyr	Gln	Val	Ala	Arg	Gly	Met	Glu
							595		600		605				

Tyr	Leu	Ala	Ser	Lys	Cys	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn
							610		615		620			

Val	Leu	Val	Thr	Glu	Asp	Asn	Val	Met	Lys	Ile	Ala	Asp	Phe	Gly	Leu
							625		630		635		640		

Ala	Arg	Asp	Ile	His	His	Ile	Asp	Tyr	Tyr	Lys	Lys	Thr	Thr	Asn	Gly
							645		650		655				

Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	Pro	Glu	Ala	Leu	Phe	Asp	Arg	Ile
							660		665		670				

Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Leu	Leu	Trp	Glu
							675		680		685				

Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	Tyr	Pro	Gly	Val	Pro	Val	Glu	Glu
							690		695		700				

Leu	Phe	Lys	Leu	Leu	Lys	Glu	Gly	His	Arg	Met	Asp	Lys	Pro	Ser	Asn
							705		710		715		720		

Cys	Thr	His	Glu	Leu	Tyr	Met	Met	Arg	Asp	Cys	Trp	His	Ala	Val
							725		730		735			

Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys	Gln	Leu	Val	Glu	Asp	Leu	Asp	Arg
							740		745		750				

Ile	Val	Ala	Leu	Thr	Ser	Asn	Gln	Glu	Tyr	Leu	Asp	Leu	Ser	Met	Pro
							755		760		765				

Leu	Asp	Gln	Tyr	Ser	Pro	Ser	Phe	Pro	Asp	Thr	Arg	Ser	Ser	Thr	Cys
							770		775		780				

Ser	Ser	Gly	Glu	Asp	Ser	Val	Phe	Ser	His	Glu	Pro	Leu	Pro	Glu	Glu
							785		790		795		800		

Pro	Cys	Leu	Pro	Arg	His	Pro	Pro	Gln	Leu	Ala	Asn	Gly	Gly	Leu	Lys
							805		810		815				

Arg Arg

<210> SEQ ID NO 24

<211> LENGTH: 3974

<212> TYPE: DNA

<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 24

cggggctatc gcggccccgc caggaccgga gcggagcccg gggggccgcgg gcccggagccg 60

aggacgcggg cgcccccccg cccgcacaag ccacggcggg ctctccagag gcggaatcgc 120

102

-continued

cgagcccagt gagagtcagc tcaccaacga ggatcaagcc cacagcagcg tctccatgga	180
ggtgtggagc ctggtcacca acctctaacc gcagaactgg gatgtgcagc tggaaagtgcc	240
tccctttctg ggctgtgctg gtcacagcca cgctctgcac ggccaggccg gctccgacct	300
cgcggaaaca agctcagccc tggggagccc ccgtggaagt ggagtecttc ctggtccacc	360
cgggtgacct gctcagcgc cgctgtcgcc tgccggacga tgttcagagc atcaactggc	420
tgcggggacgg ggtcagctg gtggaaagca accgcacccc catcacaggg gaggaggtgg	480
aggtgcggga ctccgtgccc tccgactccg gcctctacgc ctgtgtgacc agcagccct	540
cgggcagcga caccacctac ttctccgtca acgtctcaga tgctctccc tcttcggagg	600
atgacgatga cgatgatgac tcctcctcag aggagaaaaga gacagataac accaaaccaa	660
accccggtggc tccgtactgg acatccccag agaagatggaa aaagaaaatttgcatgcgg	720
cagctgccaa gacagtgaag ttcaagtgcc cctccagtgg gactcttaac cccaccttgc	780
gctggctgaa aatggcaaa gaattcaagc ctgaccacag aatcgaggc tacaagggtcc	840
gttatgccc ctggaggcatc atcatggact ccgtgggtgcc ctccgacaag ggcaactaca	900
cctgcgtcggt ggagaacggag tatggcagca tcaaccacac ctaccagctt gacgttggtgg	960
agcgggtcccc tcaccggccc atcctgcagg cagggttgcc agccaacaag acagtggccc	1020
tgggcagcaa tgtggattc atgtgcaagg tgtacagtga cccacagccc cacatccagt	1080
ggctaaagca catcgagggtg aatggggagta agattgggtcc ggacaaccta ccttatgtcc	1140
agatcttggaa gactgccggc gttataccca ccgacaaaga gatggagggtg ctccacttaa	1200
ggaatgtctc ctttgaggac gcggggggagt atacatgttttgc ggcgggttaac tctatcggac	1260
tctcccatca ctctgcatgg ttgaccgttc tggaaagccct ggaagagcgc ccggcggtga	1320
tgacctcgcc cttgtacactg gagatcatca tctactgcac aggggccttc ctcatctcct	1380
gcatgggtggc gtctgtcatc atctacaaga tgaagagtgg caccaagaag agtgaattcc	1440
acagccagat ggccgtgcac aagctggcca agagcatccc tctgcgcaga caggtgtcag	1500
ctgactccag tgcctccatg aactctgggg tccctactggg tccggccgtcg cgtctctcct	1560
ccagtgggac ccccatgctg gctgggggtct ccgaatacga gtttctgaa gaccctcgct	1620
gggagctgcc tcgggacagg ctgggttttag gcaaaccctt gggagaggc tgctttggc	1680
aggtgggttttggc ggcagaggcc attgggctgg acaaggacaa gccaaccgt gtgaccaaaag	1740
tggctgtgaa gatgtgtgaa tcggatgcaa cagagaaaga cctgtcagac ctgatctctg	1800
agatggagat gatgaagatg attgggaagc acaagaacat catcaaccctg ctggggggct	1860
geacgcagga cggacctctc tatgtcatttgc tggagttatgc ctccaaaggc aacctccgt	1920
agtacctgca ggcccgaggcc cccgcgtggcc tggaaatactg ctacaacccc agccacaacc	1980
cgaggaggca gctctctcc aaggacctgg tctctgtgc ctatcagggtg gctcgaggca	2040
tggagttactt cgtttccaaag aagtgcatac accgagaccc ggcggccagg aacgtccctg	2100
tgacggaaaga caacgtgtatg aagatcgcag actttggcct tggccggagc atccaccaca	2160
ttgactacta caaaaagaca accaacggcc gactgcccggt gaagtggatg gcaccggaaag	2220
ctttgttttga cccgatctac acccaccaga gtgacgtgtg gtctttggg gtgctccctgt	2280
gggaaatctt cactctgggc ggctcccat accctggcgct ccctgtggag gagctttca	2340
agctgttggaa ggagggtcat cggatggaca agcccaactaa ctgcacccat gaactataca	2400
tgtatgtgcg agactgttgg cacgcggtaac cctccacagag acctacccatc aagcagctgg	2460
tggaaagaccc ttgtggccatt gtggcccttga cctccaaacca ggagtatctg gacctgtcga	2520

-continued

tgccctgga ccagtactcc cccagcttcc ctgacacccg cagctctacc tgctcctctg 2580
 gggaaagttc cgtcttcctct cacgaacct tgcggaggaa gcccgcctg ccccgacacc 2640
 caccggcact tgccaacggc ggactcaaac ggcgcgtacc ggcacccctgg caccctccc 2700
 caaaactccat ccttagctgt gaccctcccc ccctcctgtc ggactctgcc ccaccccgcc 2760
 ccttcctgtc ggcaggagcc agctgcctac ctggggcctt caccggcagt tccctctcc 2820
 acctccccct cctctcagcc tgctggtgcc acagaggaaac agggaggcag gtacttgctg 2880
 aegggcaactt tgtttctcc cagtgttggaa ccaagacccc ctccccccta ccgggcaactg 2940
 cctggaggggg tgggaagtgg gggatgagca gcactcgagc gactgagcctt tccgggtttg 3000
 gttttgtctg ctccatgcag cctgtccacc cgggttctgg tggcaggtcc ttgggctaca 3060
 geagtgggtt gggggggggg cagtgttgg gcccctgcgc cagatggatg gtgccaagg 3120
 ctcttaatt ccaataactaa tgcgtttgc tgaccaaata cctggatccca gaggatggag 3180
 ttgcagaggc tggaaagcagt gtggggccccc tggggcccaag ccccaaaccg ggggcttgc 3240
 acatagctac gaagaaaaca caaagtgtat aaatctgagt atatatttac atgtctttt 3300
 aaaagggtcg ttaccagaga tttaccact gggaaagatg ctccctgggg ctgggaggca 3360
 tcgggtgcta tatattaaaa acaaagaaaa aagaaaaaaa aaaaaggaaa atgtttttaa 3420
 aaagggctata tatttttgc tacttttgc tttttttttt tttaaattat gttctaaacc 3480
 tattttcagt ttaggtccct caataaaaat tgctgctgct tcatttttat acgggctgtg 3540
 tgacgcacac gggagaggat cttggccgca aaggagcaag cgggctctgg agctgtctgt 3600
 ccagagtgcg tactatctgt ggtccctcc cactcctcac cttatgtctc actccttaggc 3660
 ctccgcacag accttggc tttggaaag gcagggaaag aagatggatg gggcaggag 3720
 cagaggcact gggcccaggg ccaggcttct cagccctcat ttccctgggg aagagaggag 3780
 gaaggggatg gggggcagaa tggggtgtga gtgtcagaca gggagctgga ggcctggcct 3840
 caaaagagcc aaggtgttagg agttcctgca gtggcacaac aggatcggtg gtgtcttgg 3900
 tgtgctggaa tgcagatttgc atccctggcc cagcacagtg ggttaaggat gggcgttgc 3960
 cgcaatgttgc actt 3974

<210> SEQ ID NO 25

<211> LENGTH: 822

<212> TYPE: PRT

<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 25

Met	Val	Ser	Trp	Gly	Arg	Phe	Ile	Cys	Leu	Val	Val	Val	Thr	Met	Ala
1									10				15		

Thr	Leu	Ser	Leu	Ala	Arg	Pro	Ser	Phe	Asn	Leu	Val	Glu	Asp	Thr	Thr
								20				25			30

Val	Glu	Pro	Glu	Glu	Pro	Pro	Thr	Lys	Tyr	Gln	Ile	Ser	Gln	Pro	Glu
								35				40			45

Val	Tyr	Val	Ala	Ala	Pro	Arg	Glu	Ser	Leu	Glu	Leu	Arg	Cys	Leu	Leu
								50				55			60

Arg	Asp	Ala	Ala	Val	Ile	Ser	Trp	Thr	Lys	Asp	Gly	Val	His	Leu	Gly
								65				70			80

Pro	Asn	Asn	Arg	Thr	Val	Leu	Ile	Gly	Glu	Tyr	Leu	Gln	Ile	Lys	Gly
								85				90			95

Ala	Thr	Pro	Arg	Asp	Ser	Gly	Leu	Tyr	Ala	Cys	Thr	Ala	Ala	Arg	Ser
								100				105			110

-continued

Val Asp Ser Glu Thr Val Tyr Phe Met Val Asn Val Thr Asp Ala Ile
 115 120 125
 Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Gly Ser Glu Asp Phe Val
 130 135 140
 Ser Glu Asn Ser Asn Ser Lys Arg Ala Pro Tyr Trp Thr Asn Thr Glu
 145 150 155 160
 Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys
 165 170 175
 Phe Arg Cys Pro Ala Gly Gly Ser Pro Thr Pro Thr Met Arg Trp Leu
 180 185 190
 Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Tyr Lys
 195 200 205
 Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser
 210 215 220
 Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Asp Tyr Gly Ser Ile
 225 230 235 240
 Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro
 245 250 255
 Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly
 260 265 270
 Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile
 275 280 285
 Gln Trp Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp
 290 295 300
 Gly Leu Pro Tyr Leu Lys Val Leu Lys His Ser Gly Ile Asn Ser Ser
 305 310 315 320
 Asn Ala Glu Val Leu Ala Leu Phe Asn Val Thr Glu Ala Asp Ala Gly
 325 330 335
 Glu Tyr Ile Cys Lys Val Ser Asn Tyr Ile Gly Gln Ala Asn Gln Ser
 340 345 350
 Ala Trp Leu Thr Val Leu Pro Lys Gln Gln Ala Pro Val Arg Glu Lys
 355 360 365
 Glu Ile Thr Ala Ser Pro Asp Tyr Leu Glu Ile Ala Ile Tyr Cys Ile
 370 375 380
 Gly Val Phe Leu Ile Ala Cys Met Val Val Thr Val Ile Leu Cys Arg
 385 390 395 400
 Met Lys Thr Thr Lys Lys Pro Asp Phe Ser Ser Gln Pro Ala Val
 405 410 415
 His Lys Leu Thr Lys Arg Ile Pro Leu Arg Arg Gln Val Thr Val Ser
 420 425 430
 Ala Glu Ser Ser Ser Met Asn Ser Asn Thr Pro Leu Val Arg Ile
 435 440 445
 Thr Thr Arg Leu Ser Ser Thr Ala Asp Thr Pro Met Leu Ala Gly Val
 450 455 460
 Ser Glu Tyr Glu Leu Pro Glu Asp Pro Lys Trp Glu Phe Pro Arg Asp
 465 470 475 480
 Lys Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
 485 490 495
 Val Met Ala Glu Ala Val Gly Ile Asp Lys Glu Lys Pro Lys Glu Ala
 500 505 510
 Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Glu Lys Asp
 515 520 525

US 9,226,960 B2

109**110**

-continued

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys		
530	535	540

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro			
545	550	555	560

Leu Tyr Val Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr		
565	570	575

Leu Arg Ala Arg Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp Val Asn		
580	585	590

Arg Val Pro Glu Glu Gln Met Thr Phe Lys Asp Leu Val Ser Cys Thr		
595	600	605

Tyr Gln Leu Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile		
610	615	620

His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asn Asn Val			
625	630	635	640

Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Ile Asn Asn Ile Asp		
645	650	655

Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala		
660	665	670

Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp		
675	680	685

Ser Phe Gly Val Leu Met Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro		
690	695	700

Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly			
705	710	715	720

His Arg Met Asp Lys Pro Ala Asn Cys Thr Asn Glu Leu Tyr Met Met		
725	730	735

Met Arg Asp Cys Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys		
740	745	750

Gln Leu Val Glu Asp Leu Asp Arg Ile Leu Thr Leu Thr Thr Asn Glu		
755	760	765

Asp Tyr Leu Asp Leu Ser Gln Pro Leu Glu Gln Tyr Ser Pro Ser Tyr		
770	775	780

Pro Asp Thr Arg Ser Ser Cys Ser Ser Gly Asp Asp Ser Val Phe Ser			
785	790	795	800

Pro Asp Pro Met Pro Tyr Glu Pro Cys Leu Pro Pro Tyr Pro Gln Arg		
805	810	815

Asn Gly Ser Val Asn Thr	
820	

<210> SEQ ID NO 26

<211> LENGTH: 2738

<212> TYPE: DNA

<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 26

tcgtccacat ggagatatgg aagaggacgg gggattggca gcgtaaccat ggtcagctgg	60
ggccgcttca tctgccttgt tttgggtcacc atggcaacct ttgtctctggc ccggccctcc	120
ttaaatttag ttgaggatac cacggtgagcc cccgaagagc cacaaccaa ataccaaatac	180
tcccaaccag aagttaacgt ggctgcgcc cgggagtcgc tagagttgcg ctgcctgttgc	240
cgagatgccc ccgtgatcag ttggactaag gatggggatc acttggggcc caacaatagg	300
acagtgccta ttggggatc cttgcagata aaagggtcca cgcctaggaa ctccggctc	360
tatgcttgcata ccgctgctag gagtgtagac agtgagactg tctacttcat ggtcaatgtc	420

-continued

acagatgcca tctcgccgg agatgacgag gacgacaccg atggctcaga ggattttgtc	480
agtgagaaca gtaacagcaa gagagccccg tactggacca acacagaaaa gatggaaaaaa	540
cggctgcacg ctgtccctgc cgccaacact gtcaagttcc gctgtccagc tgggggttagt	600
ccaacaccaa ccatgagggtg gctgaaaaac gggaaaggaat ttaagcagga acatcgatt	660
ggaggctata aggtacgaaa ccagcactgg agccctatta tggaaagcgt ggttcatcc	720
gacaaaggaa attatacctg cgtggatggag aacgattacg ggtccatcaa tcacacrtac	780
cacctcgacg tcgttgagcg atcgccgcac cggccatcc tccaagccgg actgcccggcc	840
aacgcctcca ccgtgggtgg gggcgcacgtg gagtttgtct gcaagggtgt aagtgtgcc	900
cagccccaca tccagtgat caaacacgtg gaaaagaacg gcagcaaata cggcccccac	960
gggctgcctt acctaagggt tctgaagcac tcaggataa atagttccaa tgcaagaatg	1020
ctggctctgt tcaatgtgac tgaggcgat gctggggagt atatttgtaa ggtctccat	1080
tatatagggc aggccaacca gtctgcctgg ctcactgtcc tgccaaaaca gcaagctccc	1140
gtgagagaaa aggagatcac agcttccca gactacctgg agatagccat ttactgcata	1200
ggggtgtttcc tgatcgccctg catggatggat acggtcattc tgtgcggat gaagaccacc	1260
accaagaacg cggacttcag cagccagccg gcagtgcaca agctgaccaa ggcgcattccc	1320
ctgcggagac aggtaaacgt ttctgcccgg tccagctcctt ccatgaactc caacacccca	1380
ctggtgagga ttacaactcg cctctccctcc acagcagaca ccccccgtct ggccgggttc	1440
tccgagtacg agctgcggga agatccaaag tgggagtttcc ccaagatataa gctgacgctg	1500
ggcaaaacccc tgggagaagg ttgcctttgg caagtggatca tggctgaagc ggtggaaatc	1560
gacaaagaga agcccaagga agcagtcact gtggccgtga agatgttga agatgtgcc	1620
acagagaaag accttctga tctggatgtca gagatggaga tggatgtat gattggcaaa	1680
cacaaaata tcataaatct cctcgagcc tggatgtatc atggccgtct ctacgtcata	1740
gtcgagtacg cctcgaaagg caacccctcgaa ggtacccgtc gcgcggggcg gcctccgggg	1800
atggagtaact cgtacgacgt caacccgtcg cccgaggagc agatgacctt caaggacttgc	1860
gtgtcctcgca cttaccatgt ggccgggggc atggagtaact tggcctccca aaaatgtatc	1920
catcgagatt tagccggccag aaatgttttgc gtaacagaaaa acaatgtat gaaaatagcc	1980
gacttcggac tggccagaga tatcaacaat atagactatt acaaaaagac caccaatggc	2040
cggcttcggg tcaagtgat ggctccagag gcccttttgc atcgctgtca caccacccag	2100
agtgtatgtt ggtccttcgg ggtgttaatg tggagatct tcaatgttggggctcgcccc	2160
tacccaggaa ttcccgatggaa ggaacttttgc aagctgtca aagaaggaca caggatggat	2220
aagccagcaa actgcaccaa cgaactgtat atgatgtatc gagactgttgc gcatgcgggt	2280
ccctcacaga gacccacactt caagcagtttgc gtatgtatc tggatgtatc tctcacactc	2340
acgaccaatg aggactactt ggacccgtcgt cggccatcg aacagtatttgc acctgttttgc	2400
cctgacacca ggagttcttg ctttcgatggaa gatgtatctt ttttcttcggggccatgt	2460
ccttatgaac cctgccttc tccgtatccca cagagaaacg gcagtgtttaa cacatgtatc	2520
ggcttgatccc cctgtccca gacaggccgg cggccgggggc ctatgtgtac tgagcagggg	2580
aggccatgcc tcccgaccc tggatgtatc gatgtatgttgc gtaataatttggaaacgtgg	2640
atcgccagga gcttaggtgt actgagcagg ggaggccatgttcccgccag cctgtatata	2700
tggatgtatc gagtaataatggaaacgt gatcgatggca	2738

-continued

<210> SEQ ID NO 27
<211> LENGTH: 391
<212> TYPE: DNA
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 27

```
gtcatggat ggacaagccc agtaactgca cccatgaact gtaagcatga ggagatgcct      60
ggggccctgg gtcagccct gggagggtgg gggatggcgt ggacgrgttag aggagggaaag    120
grgtgctyag ccagayaccg gggacttctt ggcacccctt cccacagtcc tccggccctg     180
agcctttttt tttttaaaac tcagtgaatt ttattacatt tatagttgta caatgatcat     240
cacaacccta agcctttttt tttttcatac tgcttcttctt ctccctcccc tgacttcacc     300
atcctgcccc agatacatgaa tgatgcgaga ctgttggcac ggggtaccct cccagagacc     360
taccttcaag cagctgggtgg aagacctgga c                                         391
```

<210> SEQ ID NO 28
<211> LENGTH: 800
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 28

```
Met Gln Leu Leu Leu Ala Leu Leu Gly Val Leu Leu Ala Val Pro Gly
1           5          10          15

Ala Pro Ala Leu Ser Leu Glu Ala Ser Glu Glu Thr Glu Leu Glu Pro
20          25          30

Cys Leu Ala Pro Ser Pro Glu Glu Gln Glu Arg Glu Leu Thr Val Val
35          40          45

Leu Gly Gln Ser Val Arg Leu Cys Cys Gly Arg Ala Glu Arg Ser Gly
50          55          60

His Trp Tyr Lys Glu Gly Ser Arg Leu Ala Pro Ala Gly Arg Val Arg
65          70          75          80

Gly Trp Arg Gly Arg Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala
85          90          95

Gly Arg Tyr Phe Cys Leu Ala Arg Gly Ser Met Leu Val Leu His Asn
100         105         110

Val Thr Leu Val Met Asp Asp Ser Met Ile Ser Ser Asn Gly Asp Glu
115         120         125

Asp Pro Gly Thr His Ser Gly Pro Ser Asn Gly His Ile Tyr Pro Gln
130         135         140

Gln Ala Pro Tyr Trp Thr His Pro Gln Arg Met Glu Lys Lys Leu His
145         150         155         160

Ala Val Pro Ala Gly Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly
165         170         175

Asn Pro Met Pro Thr Ile Arg Trp Leu Lys Asp Gly Gln Asp Phe His
180         185         190

Gly Glu Asn Arg Ile Gly Gly Ile Arg Leu Arg His Gln His Trp Ser
195         200         205

Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys
210         215         220

Leu Val Glu Asn Ser Leu Gly Ser Ile Arg Tyr Ser Tyr Leu Leu Asp
225         230         235         240

Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro
245         250         255

Ala Asn Thr Thr Ala Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys
260         265         270
```

-continued

Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Ile Val
 275 280 285
 Ile Asn Gly Ser Ser Phe Gly Ala Asp Gly Phe Pro Tyr Val Gln Val
 290 295 300
 Leu Lys Thr Ala Asp Ile Asn Ser Ser Glu Val Glu Val Leu Tyr Leu
 305 310 315 320
 Arg Asn Val Ser Ala Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly
 325 330 335
 Asn Ser Ile Gly Leu Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro
 340 345 350
 Glu Glu Asp Leu Thr Trp Thr Ala Ala Gly Pro Glu Ala Arg Tyr Thr
 355 360 365
 Asp Val Ile Leu Tyr Ala Ser Gly Ser Leu Ala Leu Leu Val Leu Leu
 370 375 380
 Leu Leu Ala Gly Leu Tyr Arg Arg Gln Val Leu His Gly Arg His Pro
 385 390 395 400
 Arg Gln Pro Ala Thr Val Gln Lys Leu Ser Arg Phe Pro Leu Ala Arg
 405 410 415
 Gln Phe Ser Leu Glu Ser Gly Ser Ser Ala Lys Ser Ser Ser Leu
 420 425 430
 Val Arg Gly Val Arg Leu Ser Ser Ser Gly Pro Pro Leu Leu Ala Gly
 435 440 445
 Leu Val Ser Leu Asp Leu Pro Leu Asp Pro Leu Trp Glu Phe Pro Arg
 450 455 460
 Asp Arg Leu Val Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln
 465 470 475 480
 Val Val Cys Ala Glu Ala Phe Gly Met Asp Pro Thr Arg Pro Asp Gln
 485 490 495
 Ala Ser Thr Val Ala Val Lys Met Leu Lys Asp Asn Ala Ser Asp Lys
 500 505 510
 Asp Leu Ala Asp Leu Val Ser Glu Met Glu Val Met Lys Leu Ile Gly
 515 520 525
 Arg His Lys Asn Ile Ile Asn Leu Leu Gly Val Cys Thr Gln Glu Gly
 530 535 540
 Pro Leu Tyr Val Ile Val Glu Cys Ala Ala Lys Gly Asn Leu Arg Glu
 545 550 555 560
 Phe Leu Arg Ala Arg Arg Pro Pro Gly Pro Asp Leu Ser Pro Asp Gly
 565 570 575
 Pro Arg Ser Ser Glu Gly Pro Leu Ser Phe Pro Ala Leu Val Ser Cys
 580 585 590
 Ala Tyr Gln Val Ala Arg Gly Met Gln Tyr Leu Glu Ser Gln Lys Cys
 595 600 605
 Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn
 610 615 620
 Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Gly Ile His His Ile
 625 630 635 640
 Asp Tyr Tyr Lys Thr Ser Asn Gly Arg Leu Pro Val Lys Trp Met
 645 650 655
 Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val
 660 665 670
 Trp Ser Phe Gly Ile Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser
 675 680 685

-continued

Pro	Tyr	Pro	Gly	Ile	Pro	Val	Glu	Glu	Leu	Phe	Ser	Leu	Leu	Arg	Glu
690						695			700						

Gly	His	Arg	Met	Asp	Arg	Pro	Pro	His	Cys	Pro	Pro	Glu	Leu	Tyr	Gly
705						710			715			720			

Leu	Met	Arg	Glu	Cys	Trp	His	Ala	Ala	Pro	Ser	Gln	Arg	Pro	Thr	Phe
725						730			735						

Lys	Gln	Leu	Val	Glu	Ala	Leu	Asp	Lys	Val	Leu	Leu	Ala	Val	Ser	Glu
740						745			750						

Glu	Tyr	Leu	Asp	Leu	Arg	Leu	Thr	Phe	Gly	Pro	Tyr	Ser	Pro	Ala	Gly
755						760			765						

Gly	Asp	Ala	Ser	Ser	Ser	Cys	Ser	Ser	Ser	Asp	Ser	Val	Phe	Ser	His
770						775			780						

Glu	Pro	Leu	Pro	Leu	Gly	Pro	Ser	Ser	Phe	Phe	Pro	Gly	Val	Gln	Thr
785					790			795			800				

<210> SEQ ID NO 29

<211> LENGTH: 2820

<212> TYPE: DNA

<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 29

atgcagctgc	tgctggccct	gttgggggtc	ctgctggcag	tgcctggggc	tccagcttg	60
tctcttgagg	cctctgagga	aacggagctg	gagccctgc	tggcccccag	cccgaggag	120
caagagcggg	agctgactgt	ggtecttggg	cagtctgtgc	ggttatgctg	tggggggct	180
gaacgtatgt	gccactggta	caaggagggt	agtcgcctgg	cacctgctgg	ccgagtagcga	240
ggctggagag	gccgtttgga	attgccagc	ttcttaccccg	aggatgctgg	ccgataacttc	300
tgccctggcac	gagggtccat	gcttgtctg	cacaatgtca	ccttggttat	ggatgactcc	360
atgatctcca	gcaacggta	tgaggacccc	gggacccaca	gtggcccttc	aatgggcac	420
atttaccccc	agcaagcacc	ctactggaca	caccccccagc	gcatggagaa	gaaactgcat	480
gcagtgcctg	ctgggaacac	tgtcaagtt	cgctgtccag	ccggcaggcaa	ccccatgccc	540
accatecgct	ggcttaagga	tggacaggac	ttccatgggg	agaatcgcat	tggaggcatt	600
aggctgcgcc	accagcaactg	gagcctggtg	atggaaagcg	tggtgecatc	ggaccgtggc	660
acatacacct	gcctctggta	gaactcttgc	ggcagcatcc	gctacagcta	tctgtcttgc	720
gtactggagc	ggtccccgca	ccggcccatc	ctgcagggcg	ggctcccagc	caataccaca	780
gccgtgtgg	gcagcgtacgt	ggagctgtta	tgcaagggtg	acagcgatgc	ccagcctcac	840
atccagtgcc	tgaagcacat	tgtcatcaac	ggcagcagct	ttggtgccga	cggtttcccc	900
tatgtcaag	tcttaaagac	agcagacatc	aatagctcg	aggtggaggt	cctataacctt	960
cgaaatgtgt	ctgcccggaa	cgcagggtaa	tacacctgtc	tggcaggcaa	ctctatccgc	1020
cttccttacc	agtcaagctt	gctcacagtg	ttgccagaag	aggacctcac	gtggacggca	1080
gcagggcccg	aggcttaggta	cacggatgtc	atccctgtacg	catcaggctc	tctggtttg	1140
cttgtgtttc	tgctgtggc	tgggtcttat	cgccggcagg	tgttccacgg	ccggcacccc	1200
cgccagcccg	ccaccgtgca	gaaactctcc	cggttccctt	tggcacgaca	gttctccctg	1260
gagtcgggct	cctcagccaa	gtcaagctcg	tctctggtg	gggggtgtcg	tctctccctc	1320
agcggccccc	cattgtcg	tggctctgt	agtcttagacc	tacctctcg	cccaactgtgg	1380
gagttccccc	gggacaggct	ggtgctcg	aagcccctgg	gtgaggggctg	cttcggcag	1440
gtgggtgttg	cagaggcctt	tggcatggac	cccacccggc	ccgatcaagc	cagcaccgt	1500

-continued

```

gctgtcaaga tgcttaagga caatgcttct gacaaggact tggctgacct agtctcttag 1560
atggaggtga tgaagctgat tggccgcacac aagaacatca tcaatctgct gggagtcgtc 1620
accaggaaag ggccccgtta cgtgattgtg gagtgtgtg ccaaggaaa cctgeggag 1680
ttcctgcccc cccgecgccc cccaggccct gacctcagcc ctgatggggc tcggagcagt 1740
gagggaccac ttcccttccc tgcctggtc tccctgcgtat atcagggtgc ccgaggcatg 1800
cagttacatgg agtcacaaaa gtgcattccac cgggacatgg ctgcccccaa cgtgtgttg 1860
actgaggaca atgtgatgaa gatcgctgac tttgggtgg cccgaggcat ccaccatatt 1920
gactactaca agaaaaacaag caacggccgc ctgcctgtca agtggatggc acctgaggcc 1980
ttgtttgaca gagtctacac acaccagat gacgtgtggt cattttggat cctgtgttg 2040
gagatcttta ccctcgcccc ctcccggtac cctggcatcc ccgtggagga gctgttcgt 2100
ctgctacggg agggccatcg gatggacccgg cccccacact gcccctccaga gttgtatgg 2160
ctgatgcgtg agtgtggca cgcagcaccc tctcagaggc ccactttcaa gcagctgttg 2220
gaggcactgg acaagggtcct gctggctgtc tctgaagagt accttgcactt ccgcctaacc 2280
tttggaccct actcccccgc cgggtggggc gccagcagct cctgctccctc cagcgactcg 2340
gtcttcagcc atgagccccct gccccctggga cccagctcct tcttccctgg ggtgcagacg 2400
tgagcggtgg caccagggtt taccagtgg ccagttggca gccttgggtc tcccgctca 2460
gccacacaacct ggtgaccccttgc gcaagccccag gtcctgactt aagggtactg tcccagattt 2520
ctgggtccgc tttggggagg tccgtctctg gtcctgggtt ccctagttga gacttccctgc 2580
tccggccctca gcttctcaag ccagaattca agtcgtctca agggccctgccc tttgccttag 2640
agtcatggtc gtagtgttct attggctttt gaggttctgc ttggcctcat gggccttgat 2700
gtttcgtctt tttcccgagg cttccgttgg tccctggctgc aggggttgcc taaatctccc 2760
tgcttcctta catcaagaga agtccctggcc tctgaaccct atttccccag gcctccccag 2820

```

<210> SEQ_ID NO 30

<211> LENGTH: 237

<212> TYPE: PRT

<213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 30

Met	Pro	His	Val	Tyr	Pro	Ser	Ser	Phe	Gly	Asp	Leu	Glu	Ile	Phe	Lys
1				5				10				15			

Ala	Cys	Ser	Asp	Thr	Glu	Ser	Ser	Leu	Asp	Ser	Asn	Phe	Ser	Thr	Leu
				20				25				30			

Gly	Trp	Lys	Arg	Leu	Leu	Arg	Phe	Glu	Thr	Leu	Ala	Gly	Lys	Lys	Met
				35			40				45				

Gly	Glu	Lys	Val	Glu	Phe	Lys	Leu	Leu	Glu	Val	Glu	Ser	Arg	Leu	Val
	50				55				60						

Ala	Gln	Gln	Lys	Pro	Arg	Thr	Ala	Arg	Gly	Pro	Arg	Gln	Gly	Pro	Gly
65				70				75				80			

Gly	Thr	Met	Ala	Ala	Gly	Ser	Ile	Thr	Thr	Leu	Pro	Ala	Leu	Pro	Glu
					85			90				95			

Asp	Gly	Gly	Ser	Gly	Ala	Phe	Pro	Pro	Gly	His	Phe	Lys	Asp	Pro	Lys
					100			105				110			

Arg	Leu	Tyr	Cys	Lys	Asn	Gly	Gly	Phe	Phe	Leu	Arg	Ile	His	Pro	Asp
					115			120				125			

Gly	Arg	Val	Asp	Gly	Val	Arg	Glu	Lys	Ser	Asp	Pro	His	Ile	Lys	Leu
					130			135				140			

-continued

Gln Leu Gln Ala Glu Glu Arg Gly Val Val Ser Ile Lys Gly Val Cys
 145 150 155 160

Ala Asn Arg Tyr Leu Ala Met Lys Glu Asp Gly Arg Leu Leu Ala Ser
 165 170 175

Lys Cys Val Thr Asp Glu Cys Phe Phe Glu Arg Leu Glu Ser Asn
 180 185 190

Asn Tyr Asn Thr Tyr Arg Ser Arg Lys Tyr Thr Ser Trp Tyr Val Ala
 195 200 205

Leu Lys Arg Thr Gly Gln Tyr Lys Leu Gly Ser Lys Thr Gly Pro Gly
 210 215 220

Gln Lys Ala Ile Leu Phe Leu Pro Met Ser Ala Lys Ser
 225 230 235

<210> SEQ ID NO 31

<211> LENGTH: 1063

<212> TYPE: DNA

<213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 31

atgccccacg	tgtaccctc	gtcttttgtt	gatttagaga	ttttcaaagc	ctgctctgac	60
acagaatctt	ccttgattc	caacttctt	actttgggtt	ggaaacggct	tctccgttt	120
gaaaacgctag	cggggaaaaa	aatgggggag	aaagttgagt	ttaaactttt	agaagtttag	180
tcacggctgg	ttgcgcagca	aaagccccgc	acggctcggt	gtccccggca	ggggccggga	240
gggaccatgg	cagccggag	catcaccacg	ctgcccgcct	tgccccagga	tggccggcagc	300
ggcgccctcc	cgcctggcca	cttcaaggac	cccaagcggc	tgtactgcaa	aaacgggggc	360
ttcttcctgc	gcattcaccc	cgacggccga	gttgacgggg	tccggagaa	gagcgaccct	420
cacatcaaat	tacaacttca	agcagaagag	agaggagttt	tgtctatcaa	aggagtgtgt	480
gctaaccgtt	accttgctat	gaaggaagat	ggaagattac	tggcttctaa	atgtgttaca	540
gatgagtgtt	tcttttttga	acgattggaa	tctaataact	acaataactt	ccggtaagg	600
aaatacacca	gttggtatgt	ggcactgaaa	cgaactgggc	aatataaact	tggatccaaa	660
acaggacctg	ggcagaaaagc	tatactttt	cttccaatgt	ctgctaagag	ctgattttaa	720
tggccacatc	taatctcatt	tcacatgaaa	gaagaagtat	attgtagaaa	tttggtaatg	780
agagtaaaag	aaaataaatg	tgtatagtc	agtttggata	attggtaaaa	caactttca	840
tctggtagta	aaatatgtaa	ccattgtccc	agtaaaagaaa	actaacaaaa	attgtgaaa	900
aatgtataga	tttccccctt	tttatatagca	tctgctgtta	cccagtgaag	cttacctaga	960
geaatgatct	ttttcatgca	tttgctttat	tcaagaaagag	gttttaaaa	tgtgcacatt	1020
tagaaacaaa	agttcttcat	ggaaatcata	tacattagaa	aat		1063

<210> SEQ ID NO 32

<211> LENGTH: 511

<212> TYPE: PRT

<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 32

Met Glu Lys Lys Leu His Ala Val Pro Ala Ala Lys Thr Val Lys Phe
 1 5 10 15

Lys Cys Pro Ser Ser Gly Thr Pro Asn Pro Thr Leu Arg Trp Leu Lys
 20 25 30

Asn Gly Lys Glu Phe Lys Pro Asp His Arg Ile Gly Gly Tyr Lys Val
 35 40 45

-continued

Arg Tyr Ala Thr Trp Ser Ile Ile Met Asp Ser Val Val Pro Ser Asp
 50 55 60

Lys Gly Asn Tyr Thr Cys Ile Val Glu Asn Glu Tyr Gly Ser Ile Asn
 65 70 75 80

His Thr Tyr Gln Leu Asp Val Val Glu Arg Ser Pro His Arg Ser Ile
 85 90 95

Leu Gln Ala Gly Leu Pro Ala Asn Lys Thr Val Ala Leu Gly Ser Asn
 100 105 110

Val Glu Phe Met Cys Lys Val Tyr Ser Asp Pro Gln Pro His Ile Gln
 115 120 125

Trp Leu Lys His Ile Glu Val Asn Gly Ser Lys Ile Gly Pro Asp Asn
 130 135 140

Leu Pro Tyr Val Gln Ile Leu Lys Thr Ala Gly Val Asn Thr Thr Asp
 145 150 155 160

Lys Glu Met Glu Val Leu His Leu Arg Asn Val Ser Phe Glu Asp Ala
 165 170 175

Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu Ser His His
 180 185 190

Ser Ala Trp Leu Thr Val Leu Glu Ala Leu Glu Glu Arg Pro Ala Val
 195 200 205

Met Thr Ser Pro Leu Tyr Leu Glu Ile Ile Tyr Cys Thr Gly Ala
 210 215 220

Phe Leu Ile Ser Cys Met Val Gly Ser Val Ile Val Tyr Lys Met Lys
 225 230 235 240

Ser Gly Thr Lys Lys Ser Asp Phe His Ser Gln Met Ala Val His Lys
 245 250 255

Leu Ala Lys Ser Ile Pro Leu Arg Arg Gln Val Thr Val Ser Ala Asp
 260 265 270

Ser Ser Ala Ser Met Asn Ser Gly Val Leu Leu Val Arg Pro Ser Arg
 275 280 285

Leu Ser Ser Ser Gly Thr Pro Met Leu Ala Gly Val Ser Glu Tyr Glu
 290 295 300

Leu Pro Glu Asp Pro Arg Trp Glu Leu Pro Arg Asp Arg Leu Val Leu
 305 310 315 320

Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val Val Leu Ala Glu
 325 330 335

Ala Ile Gly Leu Asp Lys Asp Lys Pro Asn Arg Val Thr Lys Val Ala
 340 345 350

Val Lys Met Leu Lys Ser Asp Ala Thr Glu Lys Asp Leu Ser Asp Leu
 355 360 365

Ile Ser Glu Met Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile
 370 375 380

Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu Tyr Val Ile
 385 390 395 400

Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu Gln Ala Arg
 405 410 415

Arg Pro Pro Gly Leu Glu Tyr Cys Tyr Asn Pro Ser His Asn Pro Glu
 420 425 430

Glu Gln Leu Ser Ser Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala
 435 440 445

Arg Gly Met Glu Tyr Leu Ala Ser Lys Lys Cys Ile His Arg Asp Leu
 450 455 460

Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala

465	470	475	480
Asp Phe Gly Leu Ala Arg Asp Ile His His Ile Asp Tyr Tyr Lys Lys			
485	490	495	
Lys Arg Ser Thr Ala Cys Glu Val Asp Gly Ala Arg Gly Ile Val			
500	505	510	

<210> SEQ ID NO 33
<211> LENGTH: 2890
<212> TYPE: DNA
<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 33

ttcagatgct ctccccctcct cagaggatga ttagtgcgtat gatgactcct cttcagagga	60
gaaaagagaca gataacacca aaccaaaccgc cgtagctccaa tattggacat ccccaaaaaaa	120
gatggaaaaag aaattgcattcg cggtgccagc tgccaagaca gtgaagttca aatgccttc	180
cagtggacc ccaaaccctca cactgcgtcg gttgaaaaat ggccaaagaat tcaaaccctga	240
ccacaggatt ggaggctaca aggtccgtta tgccacctgg agcatcataa tggactccgt	300
ggtgccctct gacaagggcgca actacacctg cattgtggag aatgagttatgc agccatcaa	360
ccacacccatc cagctggatcg tcgtggagcg gtccctcac ccgtccatcc tgcaagcagg	420
gttgcggcc aacaagacag tggccctggg tagcaacgtg gagttcatgt gtaaggtgt	480
cagtgcacca cagccgcata tccaggatggcata aaagcacatc gaggtgaacgg ggagcaagat	540
tggcccgac aacctgcctt atgtccagat cttgaagact gctggagttat accacccgaa	600
caaagagatg gaggtgccttc acttaagaaa tgtctccctt gaggacgcag gggagtatac	660
tgcttggcg ggttaactcta tcggactctc ccatcactct gcatgggttgc ccgttcttgc	720
agctctggaa gagaggccgg cggtgtatgc ctcggccctcg tacctggaga tcatcatcta	780
ttgcacaggc gccttcctca tctccctgcata ggttagggtcg gtcatcgatc acaagatgaa	840
gagtggcacc aagaagacgc acttccacag ccagatggct gtgcacaagc tggcaagag	900
catccctctg cgccagacagg taacagtgtc tgctgactcc agtgcgtcca tgaactctgg	960
ggttcttcgtt gttcgccat cacggcttc ctcaggatggg actcccatgc tagcagggt	1020
ctccgagatg gagttccctcg aagaccctcg ctggagatcg ctcgggaca gactggctt	1080
aggccaaaccctc ctggggagg gctgtttgg gcagggtggg ttggcagagg ccatcggtt	1140
ggacaaggac aaacccaaacc gtgtgaccaa agtggctgtg aagatgttgc agtggacgc	1200
aacagagaaa gacttgtcag acctgtatc agaaatggag atgatgaa tggatggaa	1260
gcataagaat atcatcaacc tgctggggc ctgcacgcag gacggccct tggatgtcat	1320
cgtggagatg gcttccaaagg gcaacctcg ggaggatctcg caggccggaa ggccccccgg	1380
gttggaaatac tgctacaacc ccagccacaa cccagaggag cagctctccctt ccaaggac	1440
gggtgtctgc gccttatcagg tggcccgagg catggatgtat ctggccatcc agaagtgcata	1500
acaccgagac ctggccgcca ggaatgtcctt ggtgacagag gacaatgtga tgaagatagc	1560
agactttggc ctcgcacggg acattccacca catcgactac tataaaaaga aacggtcac	1620
tgcctgtgaa gtggatggcg cccgaggatcg tggatgttgc gatctacacc caccagatgt	1680
atgtgtggtc ttccgggtt cttctgtggg agatcttcac tctggccggc tccccatacc	1740
ctgggtgtgc tggatggcgat ctttcacatc tggatgttgc gatctacacc caccagatgt	1800
ccagtaactg caccaacgcgat ctttgcacatc tggatgttgc gatctacacc caccagatgt	1860
cacagagacc cacccatcaag cagctggatcg aagacccatggc ccgcacatcgatc ccgttgcac	1920

-continued

ccaaaccaggag	gtacacctggac	ctgtccatgc	ccctggacca	gtactccccg	agctttcccgg	1980
acacccggag	ctctacatgc	tcctcagggg	aggattccgt	cttctctcat	gagccgctgc	2040
ccggagggcc	ctgcctgccc	cgacacccag	cccagttgc	caatgggggt	ctcaaacgc	2100
getgactgcc	acccacacgc	cctccccaga	ctctaccgtc	agctgttaacc	ctcacccaca	2160
geccctgcca	ggcccaactgc	ctgtccgtcc	ctgtccctt	tctgtgtgc	aggagccgc	2220
tgccttacgg	gggccttct	gtgtggcttg	ccttcacccc	gctcagtc	cctccctctc	2280
cgccctctct	ccacctgttg	gtgagagggt	caaagaggca	gatctttgt	gcccggccact	2340
tcatccccctc	ccagatgttg	gaccaagacc	cctccctgcc	accaggcaact	gcctggagggg	2400
cggggaggtgg	gagccgatga	acaggcatgc	aagtggagac	ttcctgagct	ttctctgtc	2460
agtttggct	gtttcgcctt	cacccgtaag	ccccttgcac	tctggggca	ggtgcccttgt	2520
cctcaggggct	acagcaatag	ggagggtca	gcttcgagcc	tgcatacga	gtgacctctg	2580
ctccagatgg	gtgggtccag	tggcttact	aattccgata	ctagttgt	ttgctacta	2640
aatgccttgt	accagaggat	ggtgagggtga	aggccagggt	ggggccagcg	ttgtggccct	2700
ggggccca	cccgaaactgg	gggtctgt	catagctatg	aagaaaacac	aaagtgtata	2760
aatctgagta	tatatttaca	tgtctttta	aaagggtcg	taccagagat	ttaccatcg	2820
ggtaagatgc	tcctgggtggc	tgggaggcat	cagttgtat	atattaaaaa	caaaaaaaaa	2880
aaaaaaaaaa						2890

<210> SEQ ID NO 34

<211> LENGTH: 34

<212> TYPE: PRT

<213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 34

Glu Gln Tyr Ser Pro Ser Tyr Pro Asp Thr Arg Ser Ser Cys Ser Ser
1 5 10 15

Gly Asp Asp Ser Gly Phe Ser Pro Asp Pro Met Pro Tyr Glu Pro Cys
20 25 30

Leu Pro

<210> SEQ ID NO 35

<211> LENGTH: 106

<212> TYPE: DNA

<213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 35

```
tgcggatgtt ttcacccatg taccctgaca caagaaggatc ttgtttttca ggagatgatt  
ctggtttttc tccagacccc atgccttaac aaccatgcct tcctca
```

<210> SEQ ID NO 36

<211> LENGTH: 808

<212> TYPE: PRT

<213> ORGANISM: *Macaca mulatta*

<400> SEQUENCE: 36

Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
1 5 10 15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
20 25 30

Gly Arg Val Ala Glu Val Ser Gly Pro Glu Pro Ser Gln Gln Glu Gln
35 40 45

-continued

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
 50 55 60
 Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Ala Gly
 65 70 75 80
 Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
 85 90 95
 Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
 100 105 110
 Leu Thr Gln Leu Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
 115 120 125
 Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
 130 135 140
 Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
 145 150 155 160
 Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
 165 170 175
 Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
 180 185 190
 Lys Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
 195 200 205
 Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly
 210 215 220
 Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
 225 230 235 240
 Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
 245 250 255
 Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
 260 265 270
 Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
 275 280 285
 Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
 290 295 300
 Tyr Val Thr Val Leu Lys Ser Trp Ile Ser Glu Ser Val Glu Ala Asp
 305 310 315 320
 Val Arg Leu Arg Leu Ala Asn Val Ser Glu Arg Asp Gly Glu Tyr
 325 330 335
 Leu Cys Arg Ala Thr Asn Phe Ile Gly Val Ala Glu Lys Ala Phe Trp
 340 345 350
 Leu Ser Val His Arg Pro Arg Ala Ala Glu Glu Leu Val Glu Ala
 355 360 365
 Asp Glu Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly
 370 375 380
 Phe Phe Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu
 385 390 395 400
 Arg Ser Thr Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile
 405 410 415
 Ser Arg Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser
 420 425 430
 Met Ser Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly
 435 440 445
 Glu Gly Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp
 450 455 460

-continued

Pro Lys Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu
 465 470 475 480
 Gly Glu Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile
 485 490 495
 Asp Lys Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu
 500 505 510
 Lys Asp Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met
 515 520 525
 Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu
 530 535 540
 Gly Ala Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala
 545 550 555 560
 Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly
 565 570 575
 Leu Asp Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr
 580 585 590
 Phe Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu
 595 600 605
 Tyr Leu Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn
 610 615 620
 Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu
 625 630 635 640
 Ala Arg Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly
 645 650 655
 Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val
 660 665 670
 Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu
 675 680 685
 Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu
 690 695 700
 Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn
 705 710 715 720
 Cys Thr His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala
 725 730 735
 Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg
 740 745 750
 Val Leu Thr Val Thr Ser Thr Asp Glu Tyr Leu Asp Leu Ser Ala Pro
 755 760 765
 Phe Glu Gln Tyr Ser Pro Gly Gly Gln Asp Thr Pro Ser Ser Ser Ser
 770 775 780
 Ser Gly Asp Asp Ser Val Phe Ala His Asp Leu Leu Pro Pro Ala Pro
 785 790 795 800
 Pro Ser Ser Gly Gly Ser Arg Thr
 805

<210> SEQ ID NO 37
 <211> LENGTH: 2592
 <212> TYPE: DNA
 <213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 37

ccccggccatg ggcggccctg cctgcgcctc cgcgctctgc gtggcagtgg ccatcggtgc	60
cggcgctcc tcggagtcct tggggacgga gcagcgcgtc gtggggcgag tggcagaagt	120
gtccggcccg gagcccagcc agcaggagca gttggcttcc ggcaggggg acgctgtgga	180

-continued

gctgagctgt	ccccggcccg	ggggtgttcc	catggggccc	actgtctggg	tcaaggatgg	240
cgcagggtcg	gtgccttcgg	agcgtgtct	ggtgcccccc	cagcggctgc	agggtgtgaa	300
tgcctccac	gaggactctg	gggcctacag	ctgccggcag	cggctcacac	agctctgtact	360
gtgccacttc	agtgtgcggg	tgacagatgc	tccatcctcg	ggagatgacg	aagacgggga	420
ggacgaggct	gaggacacag	gtgtggacac	agggggccct	tactggactc	ggcccgagcg	480
gatggacaag	aagctgtgg	ctgtgcggc	cgccaacacc	gtccgtttcc	gctgeccggc	540
tgccggcaac	cccactccct	ccatctctcg	gctgaagaat	ggcaaggagt	tccggggcga	600
gcaccgcatt	ggccgcata	agcttcggca	ccagcagtgg	agcctggta	tggaaaggct	660
ggtgccctcg	gaccggggca	actacacctg	cgtggtggag	aacaagtgg	gcagcatccg	720
geagacatac	acgctggacg	tgctggagcg	ctcccccgcac	cggcccatcc	tgcaggcggg	780
gtgccccggcc	aaccagacgg	cggtgctggg	cagcgatgtg	gagtttcaact	gcaagggtgt	840
cagtgtcg	cagccccaca	tccagtggct	caagcacgtg	gagggtgaatg	gcagcaaggt	900
ggggcccgac	ggcacaccct	acgtcaccgt	gctcaagtcc	tggatcagtg	agagtgtgga	960
ggccgcacgtg	gcctccggcc	tggccaatgt	gtcgaggcgg	gacggggggcg	agtacccctg	1020
tagageccacc	aatttcatag	gctgtggccga	gaaggccctt	tggctgagcg	ttcacaggcc	1080
cggagcagct	gaggaggagc	tggtgaggc	tgacgaggcg	ggcagtgtgt	acgcaggcat	1140
cctcagctac	gggggtggct	tcttcctgtt	catcctggtg	gtggcggctg	tgacgctctg	1200
cgcgcctgcgc	agcaccccca	agaaaaggct	gggctcccc	accgtgcaca	agatctcccg	1260
cttcccactc	aagcgacagg	tgtccctgga	gtccaaacgcg	tccatgagct	ccaacacacc	1320
gtctggcgc	atcgaaggc	tgtcttcagg	ggagggtccc	acgtggcca	atgtctccga	1380
gttttagctg	cctgtgtacc	ccaaatggga	gctgtctcg	gcccggttga	ccctgggcaa	1440
gcccccttggg	gagggtgtct	tggccaggt	ggtcatggc	gaggctatcg	gcattgacaa	1500
ggaccggggcc	gccaaggctg	tcaccgtac	cgtgaagatg	ctgaaagatg	atgccactga	1560
caaggacactg	ttagacactgg	tgtctgagat	ggagatgtg	aagatgttg	ggaaacacaa	1620
gaacattatac	aacctgctgg	gcgcctgcac	gcagggggg	cccctgtacg	tgtctgggta	1680
gtacgeggcc	aaaggcaacc	tgaggaggat	tctgcccccc	ggggccctgg	cgggccctgg	1740
ctactcttc	gacacctgca	agccgcctga	ggagcaactc	accttcaagg	acctgggtgtc	1800
ctgtgcctac	cagggtggcc	gaggcatgga	gtacctcgcc	tcccagaagt	gcatccacag	1860
ggacctggct	gctcgaaatg	tgctgggtac	cgaggacaac	gtgtatgaa	tcgcagactt	1920
cgggctggcc	cgcgcacgtc	acaaccttga	ctactacaag	aagacaacca	acggccggct	1980
gcccgtgaag	ttgatggcgc	ctgaggccct	gttgcacca	gtctacaccc	accagagtg	2040
cgtctggtcc	tttgggggtcc	tgctctggga	gatcttcacg	ctggggggct	ctccgtaccc	2100
cggcatccct	gtggaggagc	tcttcaagct	gctgaaggag	ggtcacccgga	tggacaagcc	2160
ggccaaactgc	acacacgacc	tgtacatgtat	catgcgggag	tgctggcatg	ctgcgcctc	2220
caagaggccc	accttcaagc	agctggtgg	ggacctggac	cgtgtctctca	ctgtgacgtc	2280
caccgacgag	tacctggacc	tgtcagcgc	cttcgagcag	tactcccccg	gcggccagga	2340
caccccgagc	tccagctct	cagggatga	ctccgtgttt	gccccacgacc	tgctgcccc	2400
ggccccaccc	agcagtgggg	gctcgccgac	gtgaaggccc	actggcccc	aacaatgtga	2460
gggggtccct	agcagcctac	cctgtgtctg	gtgcacagcc	actccccggc	atgagactca	2520

-continued

gtgcagatgg agagacagct acacaaagct tcagtctgtg tgcateccgtg tgtgtgtctg 2580

cgtgcgtgtg ca 2592

<210> SEQ ID NO 38

<211> LENGTH: 802

<212> TYPE: PRT

<213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 38

Met	Arg	Leu	Leu	Ser	Ala	Leu	Leu	Gly	Val	Leu	Leu	Ser	Val	Pro	Gly
1															
															15

Pro	Pro	Val	Leu	Ser	Leu	Glu	Ala	Ser	Glu	Glu	Val	Glu	Leu	Glu	Pro
															30
20															25

Cys	Leu	Ala	Pro	Ser	Met	Glu	Gln	Gln	Glu	Leu	Thr	Val	Ala		
															45
35															40

Leu	Gly	Gln	Pro	Val	Arg	Leu	Cys	Cys	Gly	Arg	Ala	Glu	Arg	Gly	Gly
															60
50															55

His	Trp	Tyr	Lys	Glu	Gly	Ser	Arg	Leu	Ala	Pro	Ala	Gly	Arg	Val	Arg
															80
65															75

Gly	Trp	Arg	Gly	Arg	Leu	Glu	Ile	Ala	Ser	Phe	Leu	Pro	Glu	Asp	Ala
															95
85															90

Gly	Arg	Tyr	Leu	Cys	Leu	Ala	Arg	Ala	Ser	Met	Ile	Val	Leu	Gln	Asn
															110
100															105

Leu	Thr	Leu	Thr	Ile	Asp	Asp	Ser	Leu	Thr	Ser	Ser	Asn	Asp	Asp	Glu
															125
115															120

Asp	Pro	Gln	Ser	His	Arg	Asp	Ser	Ser	Asn	Gly	His	Ile	Tyr	Pro	Gln
															140
130															135

Gln	Ala	Pro	Tyr	Trp	Thr	His	Pro	Gln	Arg	Met	Glu	Lys	Lys	Leu	His
															160
145															150

Ala	Val	Pro	Ala	Gly	Asn	Thr	Val	Lys	Phe	Arg	Cys	Pro	Ala	Ala	Gly
															175
165															170

Asn	Pro	Thr	Pro	Thr	Ile	Arg	Trp	Leu	Lys	Asp	Gly	Gln	Ala	Phe	His
															190
180															185

Gly	Glu	Asn	Arg	Ile	Gly	Gly	Ile	Arg	Leu	Arg	His	Gln	His	Trp	Ser
															205
195															200

Leu	Val	Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	Thr	Tyr	Thr	Cys
															220
210															215

Leu	Val	Glu	Asn	Ala	Val	Gly	Ile	Ile	Arg	Tyr	Asn	Tyr	Leu	Leu	Asp
															240
225															230

Val	Leu	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro
															255
245															250

Ala	Asn	Thr	Thr	Ala	Val	Val	Gly	Ser	Asp	Val	Glu	Leu	Cys	Lys	
															260
260															265

Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val
															275
275															280

Ile	Asn	Gly	Ser	Ser	Phe	Gly	Ala	Asp	Gly	Phe	Pro	Tyr	Val	Gln	Val
															290
290															295

Leu	Lys	Thr	Ala	Asp	Ile	Asn	Ser	Ser	Glu	Val	Glu	Val	Leu	Tyr	Leu
															305
305															310

Arg	Asn	Val	Ser	Ala	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly
															325
325															330

Asn	Ser	Ile	Gly	Leu	Ser	Tyr	Gln	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro
															340
340															345

Glu Glu Asp Leu Thr Trp Thr Ala Ala Thr Pro Glu Ala Arg Tyr Thr

-continued

355	360	365
Asp Val Ile Leu Tyr Ala Ser Gly Ser Leu Ala Leu Ala Val Leu Leu		
370	375	380
Leu Leu Ala Gly Leu Tyr Arg Gly Gln Ala Leu His Gly Arg His Pro		
385	390	395
Arg Pro Pro Ala Thr Val Gln Lys Leu Ser Arg Phe Pro Leu Ala Arg		
405	410	415
Gln Phe Ser Leu Glu Ser Gly Ser Ser Lys Ser Ser Ser Ser Leu		
420	425	430
Val Arg Gly Val Arg Leu Ser Ser Gly Pro Ala Leu Leu Ala Gly		
435	440	445
Leu Val Ser Leu Asp Leu Pro Leu Asp Pro Leu Trp Glu Phe Pro Arg		
450	455	460
Asp Arg Leu Val Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln		
465	470	475
Val Val Arg Ala Glu Ala Phe Gly Met Asp Pro Ala Arg Pro Asp Gln		
485	490	495
Ala Ser Thr Val Ala Val Lys Met Leu Lys Asp Asn Ala Ser Asp Lys		
500	505	510
Asp Leu Ala Asp Leu Val Ser Glu Met Glu Val Met Lys Leu Ile Gly		
515	520	525
Arg His Lys Asn Ile Ile Asn Leu Leu Gly Val Cys Thr Gln Glu Gly		
530	535	540
Pro Leu Tyr Val Ile Val Glu Cys Ala Ala Lys Gly Asn Leu Arg Glu		
545	550	555
Phe Leu Arg Ala Arg Arg Pro Pro Gly Pro Asp Leu Ser Pro Asp Gly		
565	570	575
Pro Gln Ser Ser Glu Gly Pro Leu Ala Phe Pro Val Leu Val Ser Cys		
580	585	590
Ala Tyr Gln Val Ala Arg Gly Met Gln Tyr Leu Glu Ser Arg Lys Cys		
595	600	605
Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn		
610	615	620
Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Gly Ile His His Ile		
625	630	635
Asp Tyr Tyr Lys Thr Ser Asn Gly Arg Leu Pro Val Lys Trp Met		
645	650	655
Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val		
660	665	670
Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser		
675	680	685
Pro Tyr Pro Gly Ile Pro Val Glu Leu Phe Ser Leu Leu Arg Glu		
690	695	700
Gly His Arg Met Asp Arg Pro Pro His Cys Pro Pro Glu Leu Tyr Gly		
705	710	715
Leu Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe		
725	730	735
Lys Gln Leu Val Glu Ala Leu Asp Lys Val Leu Leu Ala Val Ser Glu		
740	745	750
Glu Tyr Leu Asp Leu Arg Leu Thr Phe Gly Pro Tyr Ser Pro Ala Gly		
755	760	765
Gly Asp Thr Ser Ser Thr Cys Ser Ser Asp Ser Val Phe Ser His		
770	775	780

-continued

Asp	Pro	Leu	Pro	Leu	Gly	Ser	Ser	Ser	Phe	Pro	Phe	Gly	Ser	Gly	Val
785				790				795				800			

Gln Thr

<210> SEQ ID NO 39

<211> LENGTH: 2901

<212> TYPE: DNA

<213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 39

agtttgtggg	aagtccagcc	tggccctgt	agagctgcgg	gaaggagatg	cggctgctgt	60
cggcccttctt	gggggtcctg	ctgagtggtc	ctgggcctcc	agtcttgc	ctggaggcct	120
cgaggagaat	ggagctggag	ccctgcctgg	ctcccaagcat	ggagcagcaa	gagcaggagc	180
tgacagtagc	ccttgggcag	cctgtgcggc	tgtgctgtgg	gcgggctgag	cgtggtgccc	240
actggtacaa	ggagggcagt	cgcctggcac	ctgtggccg	tgtacggggc	tggaggggcc	300
gccttagat	tgccagcttc	ctacctgagg	atgctggccg	ctatcttc	ctggcccgag	360
cctccatgt	cgtccgtcaa	aatctcacct	tgactataga	tgactcttg	acctccagca	420
acgatgatga	ggaccccccag	tccataggg	actcctcgaa	tggcacatt	taccccccagc	480
aagcaccccta	ctggacacac	ccccagcgca	tggagaagaa	actgcacatgc	gtaccggctg	540
ggAACACCGT	caagttccgc	tgtccggctg	caggcaaccc	cacggccacc	atccgctggc	600
ttaaggatgg	acaggcctt	catggggaga	accgcattgg	aggcattgg	ctgcgccacc	660
agcactggag	tctcgtatgc	gagagcgtgg	tgcctcgga	ccgcggcaca	tacacttgcc	720
tgggtggagaa	cgtgtgggc	atcatccgt	ataactacct	gctggatgtg	ctggagcggt	780
ccccgcacccg	gccccatctg	caggctgggc	tcccgccaa	caccacagcc	gtgggtggca	840
gtgacgtgga	gctgtgtgc	aagggttaca	gcgtatgc	gccccacatc	cagtggctga	900
agcacatcg	catcaacggc	agcagcttcg	ggggcggacgg	cttcccttat	gtgcaagtcc	960
tgaagactgc	agacatcaat	agctcagagg	tggaggctt	gtacactgcgg	aacgtgtcag	1020
ccgaggacgc	aggcgagtac	acctgccttg	caggcaattc	catcgccctc	tcctaccagt	1080
ctgcctggct	cacgggtctg	ccagaggagg	acctcacatg	gaccgcacga	acgccccagg	1140
ccaggatatac	ggacgtcatc	ctgtacgcgt	cgggctccct	ggccttggct	gtgctctgc	1200
tgcgtggccgg	gctgtatcga	gggcaggcgc	tccacggccg	gcaccccccgc	ccacccggcca	1260
ccgtgcagaa	gctctccgc	ttccctctgg	cccgacagt	ctccctggag	tcaggctt	1320
ccagcaagtc	aagctcatcc	ctggtgcgag	gcgtgcgtct	ctccctccagc	ggccccgcct	1380
tgcgtgcggg	cctcgtgagt	ctagacctac	ctctcgaccc	actgtggag	ttccccccgg	1440
acaggctgg	gcttgggaag	ccccctggcg	agggctgttt	tggacaggta	gtacgtgcag	1500
aggccttgg	catggccct	gcggccctg	accaaggcc	tactgtggct	gtcaagatgc	1560
tcaaagacaa	cgcctctgac	aaggacctgg	ctgacctgg	ctcgagatg	gagggtatga	1620
agctgattgg	ccgacacaaag	aacatcatca	acctgctggg	tgtctgcacc	caggaaggcc	1680
ccctgtatgt	aatcgtggag	tgcgtgc	aggaaacacct	tgcggagtcc	ctgcggggccc	1740
ggcgcccccc	gggcctgac	ctcagccgg	acggctctca	gagcagtgg	ggggccactcg	1800
cctccctgg	cctggcttcc	tgcgtctacc	agggtggcccg	aggcatgcag	tatctggagt	1860
cccgaaatgt	tatccacccg	gacctggctg	cccgcaatgt	gctggtgacg	gaggacaatg	1920
tgtatgaat	agctgacttt	gggtggcc	gtggcatcca	ccacattgac	tactataaga	1980

-continued

```

aaaccagcaa cggccgcctg cctgtcaagt gnatggcgcc cgaggccttg tttgaccgag    2040
tgtacacaca ccagagtgcgt gtgtggtctt ttggggctt gctgtggag atcttcaccc    2100
tcgggggctc cccgtatccct ggcatcccg tggaggagct gttctactg ctgcgggagg    2160
gacatcgat ggaccgaccc ccacactgcc ccccagagct gtacgggctg atgcgtgagt    2220
gttggcatgc agcacccctcc cagaggccca cttcaagca gctggtggag ggcgtggaca    2280
aggtcttaact ggccgtctct gaggagtacc tgcacccctcc cctgaccccttc ggaccctatt 2340
ccccctgtgg tggggacacc agcagcacct gtcctccag tgactccgtc ttcagccacg    2400
acccctgtcc actggggatcc agtccttcc ccttgggtc tggggtgcaag acatgagtaa    2460
ggctcaaggc tgcaggca cataaacttag tggccttggg cttggggct cagccacagc    2520
ctggcacagt gtcgtacccctt ggcagcacgg ggtccctggc ccagagtgtc gtcccggtc    2580
caaggccgtg cccttgcctt tggcgctgca gtgcctgtgt cctgatgggc caaacgtcag    2640
ggttctgtcc ggcccttggg ccttggcgct cagccccccat ctcaggtttgcgtgactgctg 2700
gttggagagc tgctatgcta aatctccctgc ctcccaatac cagcaggggg ttcagggct    2760
ctgaaccccc tttccccaca ctcctccctg ctgcctgccc cagcgtcttgcgtgactgctg 2820
cgccccctga gccagagaa gctggaaagcc cgccaaaaac aggagcaaat ggcgttctat    2880
aaattatttt tttgaataa a                                         2901

```

<210> SEQ ID NO 40

<211> LENGTH: 154

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 40

Met	Ala	Ala	Ser	Gly	Ile	Thr	Ser	Leu	Pro	Ala	Leu	Pro	Glu	Asp	Gly
1								10							15

Gly	Ala	Ala	Phe	Pro	Pro	Gly	His	Phe	Lys	Asp	Pro	Lys	Arg	Leu	Tyr
								20							30

Cys	Lys	Asn	Gly	Gly	Phe	Phe	Leu	Arg	Ile	His	Pro	Asp	Gly	Arg	Val
								35							45

Asp	Gly	Val	Arg	Glu	Lys	Ser	Asp	Pro	His	Val	Lys	Leu	Gln	Leu	Gln
								50							60

Ala	Glu	Glu	Arg	Gly	Val	Val	Ser	Ile	Lys	Gly	Val	Cys	Ala	Asn	Arg
								65							80

Tyr	Leu	Ala	Met	Lys	Glu	Asp	Gly	Arg	Leu	Leu	Ala	Ser	Lys	Cys	Val
								85							95

Thr	Glu	Glu	Cys	Phe	Phe	Glu	Arg	Leu	Glu	Ser	Asn	Asn	Tyr	Asn
								100						110

Thr	Tyr	Arg	Ser	Arg	Lys	Tyr	Ser	Ser	Trp	Tyr	Val	Ala	Leu	Lys	Arg
								115							125

Thr	Gly	Gln	Tyr	Lys	Leu	Gly	Ser	Lys	Thr	Gly	Pro	Gly	Gln	Lys	Ala
								130							140

Ile	Leu	Phe	Leu	Pro	Met	Ser	Ala	Lys	Ser
								145	

<210> SEQ ID NO 41

<211> LENGTH: 695

<212> TYPE: DNA

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 41

-continued

ggccccgggc	cgttgtacac	tcaaggggct	ctctcggtt	caggaagagt	ccggctgcac	60
tgggctggga	ccccggcggg	acacggactg	ggaggcgtggc	agccccgggg	cgagccgcgc	120
tggggggccg	aggccggggt	cggggccggg	gagccccaaag	agctgccaca	gcggggtccc	180
ggggccgccc	aaggccatg	gctgccageg	gcatcacctc	gcttcccgca	ctgcccggagg	240
acggcggcgc	cgccttccca	ccaggccact	tcaaggacc	caagcggctc	tactgcaaga	300
acggcggcct	tttcctgcgc	atccatcccg	acggccgcgt	ggatggcgtc	cgcgagaaga	360
gcgaccacaca	cgtcaaacta	caactccaag	cagaagagag	aggagttgtg	tctatcaagg	420
gagtgtgtgc	caaccggta	cggcttatga	aggaagatgg	acggctgcgt	gcttctaagt	480
gtgttacaga	agagtgtttc	ttctttgaac	gactgaaatc	taataactac	aataacttacc	540
ggtcacggaa	atactccagt	tggtatgtgg	cactgaaaacg	aactggcag	tataaactcg	600
gatccaaaac	gggacctgga	cagaaggcca	tactgttct	tccaatgtct	gctaagagct	660
gactcactt	tgacactgtc	actgagacac	tgtca			695

<210> SEQ_ID NO 42

<211> LENGTH: 822

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 42

Met	Trp	Gly	Trp	Lys	Cys	Leu	Leu	Phe	Trp	Ala	Val	Leu	Val	Thr	Ala
1				5				10			15				

Thr	Leu	Cys	Thr	Ala	Arg	Pro	Ala	Pro	Thr	Leu	Pro	Glu	Gln	Ala	Gln
	20				25				30						

Pro	Trp	Gly	Val	Pro	Val	Glu	Val	Glu	Ser	Leu	Leu	Val	His	Pro	Gly
	35				40				45						

Asp	Leu	Leu	Gln	Leu	Arg	Cys	Arg	Leu	Arg	Asp	Asp	Val	Gln	Ser	Ile
	50				55				60						

Asn	Trp	Leu	Arg	Asp	Gly	Val	Gln	Leu	Val	Glu	Ser	Asn	Arg	Thr	Arg
	65				70			75		80					

Ile	Thr	Gly	Glu	Val	Glu	Val	Arg	Asp	Ser	Ile	Pro	Ala	Asp	Ser	
	85				90				95						

Gly	Leu	Tyr	Ala	Cys	Val	Thr	Ser	Ser	Pro	Ser	Gly	Ser	Asp	Thr	Thr
	100				105				110						

Tyr	Phe	Ser	Val	Asn	Val	Ser	Asp	Ala	Leu	Pro	Ser	Ser	Glu	Asp	Asp
	115				120				125						

Asp	Asp	Asp	Asp	Ser	Ser	Ser	Glu	Glu	Lys	Glu	Thr	Asp	Asn	Thr	
	130				135			140							

Lys	Pro	Asn	Arg	Arg	Pro	Val	Ala	Pro	Tyr	Trp	Thr	Ser	Pro	Glu	Lys
	145				150			155		160					

Met	Glu	Lys	Leu	His	Ala	Val	Pro	Ala	Ala	Lys	Thr	Val	Lys	Phe	
	165				170				175						

Lys	Cys	Pro	Ser	Ser	Gly	Thr	Pro	Asn	Pro	Thr	Leu	Arg	Trp	Leu	Lys
	180				185				190						

Asn	Gly	Lys	Glu	Phe	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val
	195				200				205						

Arg	Tyr	Ala	Thr	Trp	Ser	Ile	Ile	Met	Asp	Ser	Val	Val	Pro	Ser	Asp
	210				215			220							

Lys	Gly	Asn	Tyr	Thr	Cys	Ile	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	Asn
	225				230			235		240					

His	Thr	Tyr	Gln	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile
	245				250			255		255					

-continued

Leu Gln Ala Gly Leu Pro Ala Asn Lys Thr Val Ala Leu Gly Ser Asn
 260 265 270
 Val Glu Phe Met Cys Lys Val Tyr Ser Asp Pro Gln Pro His Ile Gln
 275 280 285
 Trp Leu Lys His Ile Glu Val Asn Gly Ser Lys Ile Gly Pro Asp Asn
 290 295 300
 Leu Pro Tyr Val Gln Ile Leu Lys Thr Ala Gly Val Asn Thr Thr Asp
 305 310 315 320
 Lys Glu Met Glu Val Leu His Leu Arg Asn Val Ser Phe Glu Asp Ala
 325 330 335
 Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu Ser His His
 340 345 350
 Ser Ala Trp Leu Thr Val Leu Glu Ala Leu Glu Glu Arg Pro Ala Val
 355 360 365
 Met Thr Ser Pro Leu Tyr Leu Glu Ile Ile Ile Tyr Cys Thr Gly Ala
 370 375 380
 Phe Leu Ile Ser Cys Met Leu Gly Ser Val Ile Ile Tyr Lys Met Lys
 385 390 395 400
 Ser Gly Thr Lys Ser Asp Phe His Ser Gln Met Ala Val His Lys
 405 410 415
 Leu Ala Lys Ser Ile Pro Leu Arg Arg Gln Val Thr Val Ser Ala Asp
 420 425 430
 Ser Ser Ala Ser Met Asn Ser Gly Val Leu Leu Val Arg Pro Ser Arg
 435 440 445
 Leu Ser Ser Ser Gly Thr Pro Met Leu Ala Gly Val Ser Glu Tyr Glu
 450 455 460
 Leu Pro Glu Asp Pro Arg Trp Glu Leu Pro Arg Asp Arg Leu Val Leu
 465 470 475 480
 Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val Val Leu Ala Glu
 485 490 495
 Ala Ile Gly Leu Asp Lys Asp Lys Pro Asn Arg Val Thr Lys Val Ala
 500 505 510
 Val Lys Met Leu Lys Ser Asp Ala Thr Glu Lys Asp Leu Ser Asp Leu
 515 520 525
 Ile Ser Glu Met Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile
 530 535 540
 Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu Tyr Val Ile
 545 550 555 560
 Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu Gln Ala Arg
 565 570 575
 Arg Pro Pro Gly Leu Glu Tyr Cys Tyr Asn Pro Ser His Asn Pro Glu
 580 585 590
 Glu Gln Leu Ser Ser Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala
 595 600 605
 Arg Gly Met Glu Tyr Leu Ala Ser Lys Lys Cys Ile His Arg Asp Leu
 610 615 620
 Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala
 625 630 635 640
 Asp Phe Gly Leu Ala Arg Asp Ile His His Ile Asp Tyr Tyr Lys Lys
 645 650 655
 Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu
 660 665 670

-continued

Phe Asp Arg Ile Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val
675 680 685

Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Val
690 695 700

Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp
705 710 715 720

Lys Pro Ser Asn Cys Thr Asn Glu Leu Tyr Met Met Met Arg Asp Cys
725 730 735

Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu
740 745 750

Asp Leu Asp Arg Ile Val Ala Leu Thr Ser Asn Gln Glu Tyr Leu Asp
755 760 765

Leu Ser Ile Pro Leu Asp Gln Tyr Ser Pro Ser Phe Pro Asp Thr Arg
770 775 780

Ser Ser Thr Cys Ser Ser Gly Glu Asp Ser Val Phe Ser His Glu Pro
785 790 795 800

Leu Pro Glu Pro Cys Leu Pro Arg His Pro Thr Gln Leu Ala Asn
805 810 815

Ser Gly Leu Lys Arg Arg
820

<210> SEQ_ID NO 43

<211> LENGTH: 5008

<212> TYPE: DNA

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 43

```

agccctcgcg cctcgccggc gcacagcgct cggagcgctc ctgcgggtac tttggcgcccc 60
ctctccgctg cggggcgccgc ggaacggggag cgggaacctt ggtgcagcccg ctgcgtgcag 120
aggaccgggg ctgcgcaggg aagcggggcc gagacgtccg gactggactg agactgtgct 180
tagcgcattt cggcgaccc tcgcattttcccg gcccgcagcc cgccgcgcag ctggaaaagc 240
agcggagacc gaggactttt ctcaggccc acggggcgac cacagccgtg ctgcagtcaa 300
tgcacgcggg agccccagga ggggtgatgg aactcgggctt gccagaagcc tgagacgccc 360
ccacccgcgc cgctgcgtac tggagagcgg gggggcgacac atctggggac cccggggccgc 420
ggacccggcc cctccccccc gccccgcctc cggggccacca gttccggctc cattgttccc 480
gccccggctg gagggccccg gtcggagtg ccggccggag tcgtgcctcg gcccggagcc 540
cctcgagacc ccatcaggat ctgaacggag cccggagacg agcggggggaa ggcgaagaca 600
cagacaccccg cccgcgcacg gcgagcttc cagaggcgcc accgcagccg caagtggag 660
tcagcttgcg aaggcagacc acgctcacgg tggaatatcc atggaggtac ggacccctgt 720
taccaacccctc taaccgcaga actggatgt ggggctggaa gtgcctccctc ttctgggctg 780
tgctggtcac agccactctc tgcactgcca ggcacggccc aaccttgctt gaacaagctc 840
agccctgggg agtccctgtg gaagtggagt ctctccctgg ccacccctggc gacctgtac 900
agcttcgctg tcggcttcgc gatgtgtgc agagcatcaa ctggctgcgg gatgggggtc 960
agctgggtgg a gaccaaccgt acccgcatca cagggggagga ggtggagggtg cgggactcca 1020
tccccgctga ctctggccctc tacgcttgcg tgaccagcag cccctctggc agcgataccaa 1080
cttacttctc cgtcaatgtc tcagatgcac tcccatctc ggaagatgt gacgcacgcg 1140
atgacttctc ctcggaggag aaagagacgg acaacaccaa accaaaccgtt aggctgttag 1200
ctccctactg gacatccccca gagaaaatgg agaagaaaact gcatgcgggtg cccgcgtcc 1260

```

-continued

agacggtaaa gttcaagtgc ccgtcgagtg ggacacccaa ccccactctg cgctgggtga	1320
aaaatggcaa agagtttaag cctgaccacc gaattggagg ctacaagggtt cgctatgcca	1380
cctggagcat cataatggat tctgtggtgc cttctgacaa gggcaactac acctgcatcg	1440
tggagaatga gtatgggagc atcaaccaca cctaccagct tgacgtcgta gaacgatctc	1500
cgcacccgacc catccttcag gcagggctgc ctgccaacaa gacagtggcc ctggcagca	1560
atgtggagtt catgtgtaag gtgtacagcg atccgcagcc tcacattcag tggctgaagc	1620
acatecgaggt gaaecccggaa aagatccggc cagacaactt gccgtatgtc cagatccgt	1680
agactgctgg agttaataacc accgcacaagg aaatggaggt gtttcatcta cggaatgtct	1740
cctttgagga tgcgggggag tatacgtgtc tggcgggtaa ctctatcgga ctctccatc	1800
actctgcatg gttgaccgtt ctggaagccc tggaaagagag accagctgtg atgacccatc	1860
cgctctaccc ggagatcatt atctactgca cccggggcctt cctgatctcc tgcgtgttgg	1920
gtctctgtcat catctataag atgaagagcg gcaccaagaa gagcgcacttc catagccaga	1980
tggctgtgca caagctggcc aagagcatcc ctctgcgcag acaggtaaca gtgtcagctg	2040
actccagtc acatccatgaa tctggggttc tcttgggtcg gcccctcacgg ctctcttcca	2100
ggggggacccc catgtggct ggagtctccg aatatgagct cccctggat ccccgcttgg	2160
agctgccacg agacagactg gtcttaggca aaccacttgg cgagggctgc ttccggcagg	2220
tgggtttggc tgaggccatc gggctggata aggacaaacc caaccgtgtg accaaagtgg	2280
ccgtgaagat gttgaagtcc gacgcacacgg agaaggaccc gtcggatctg atctcgagaa	2340
tggagatgt gaaaatgatt gggaaagcaca agaatatcat caaccttctg ggagegtgca	2400
cacaggatgg tcctctttat gtcattgtgg agtacgcctc caaaggcaat ctccggagtt	2460
atctacaggc ccggaggcct cctgggctgg agtactgcta taaccccagc cacaaccccg	2520
aggaacagct gtctccaaa gatctggat cctgtgccta tcaggtggct cggggcatgg	2580
agtatcttgc ctctaagaag tgtatacacc gagacctggc tgcttagaaac gtccctggta	2640
ccgaggataa cgtaatgaag atcgcagact ttggcttagc tcgagacatt catcatatcg	2700
actactacaa gaaaaccacc aacggccggc tgcctgtgaa gtggatggcc cctgaggcgt	2760
tgtttgaccg gatctacaca caccagagcg atgtgtggtc ttttggagtg ctcttgggg	2820
agatcttcac tctgggtggc tccccatacc cccgtgtgcc tgtggaggaa ctttcaagc	2880
tgcgtgaagga gggcatcgat atggacaagc ccagtaactt taccaatgag ctgtacatga	2940
tgtatgcggga ctgctggcat gcagtgcctt ctcagagacc tacgttcaag cagttgggg	3000
aagacctgga ccgcattgtg gccttgcacct ccaaccaggaa gtatctggac ctgtccatata	3060
cgctggacca gtactcaccc agctttcccg acacacggag ctccacactgc tcctcagggg	3120
aggactctgt cttctctcat gaggcgttac ctgaggagcc ctgtctgcct cgacacccca	3180
cccagcttc cAACAGTGGAA CTCAAACCGC GCTGACTACC AACCCGTCC CCAGTTTCT	3240
cccatccctgt cgtcacccgt gcccctcacc cacaatcccc ttgttggaca cactgcctt	3300
ctctctctcc ttggcgctg gcaagagcca gtgcctgact gaggccttcc tgggttgg	3360
ccttccccctt ccataccccc caagacccctt cttctccctt ttcttagcct gctgtgtgag	3420
agaggagccaa agaggcaggt gcttgcgcac ggccgcattcc tccttcccgat gtgttggacc	3480
aagacccggcc cccgtgcctg gcactgcttgc gaggtgtgca gagcggaaagc aagtggagca	3540
tccggggcat tcctgttgcac ccatcagccc cttctgttctt ggccggcagggg gccttgggg	3600

US 9,226,960 B2

151**152**

-continued

tcccttggaa	cgtaggggttt	ctgttttaggc	cttaaccgaa	ggcaacctct	gctccagatg	3660
gatgggtacca	gtagtttctt	aattccaata	ctaatttgct	ttgtgtacca	aatacctgcc	3720
tggtaccaga	agacagggag	gcagagactg	ggagccgtga	tgtgccttg	ggctgagccc	3780
tagacttggg	gctctgtaca	tagctatgaa	aaaaaacaca	aagtgtataa	atcttgagta	3840
tatatttaca	tgtctttta	aaaagggtcg	ttactagaga	tttacccatg	ggggagacgc	3900
ccagggttagc	atccgttgct	atataaaaa	aacaaacgaa	cagaaagaaa	aaaaaaagga	3960
aatatgtttt	taaaaggtca	tatattttt	tgctacttt	gctgtttat	tttttaat	4020
tatgttttaa	acctattttc	agtttaggtt	tccctcaata	aaaaattgct	gctgtttcat	4080
ttttatcctg	ggcgtgtgaa	aagagagcag	gtgtccagcg	cagaggaggg	agacaggggg	4140
taaaggccca	ttagctggtc	ttccccctgc	cccccatgac	ctctgtctcc	tggattgtgc	4200
cccagaccc	ccagccaagc	cttctatctc	ccgatgcatt	ggaaacagca	ggagaagact	4260
gagggtcctga	gggcagagag	ccaagctcgc	acacttgatt	gttccctcgg	aggagagagt	4320
gagaggatga	gtttagccag	agggttagaaac	tggtacagaaa	cccaaaccct	agaccctgta	4380
cattcagatg	tcttgtctat	cttccccaac	ctactcctca	tattcctctc	ctgtaaatat	4440
cctccccc	cctgttggtc	tctgttaccc	agttgggtct	gtccctgagc	ttggcttcct	4500
atagttttc	cttcacaaac	tccacccatc	cctcaggaaa	cagaaaacga	tctcttttgt	4560
tggggtcaac	ttggcaactc	aattctgcca	cctgctggtt	gtttgggtac	tttggctctc	4620
tattcaaacc	cacaccactc	aagccttaga	gggtttgtt	ttgtttttt	tttggtttgtt	4680
tgggtggttg	gttggctttt	ttttctggg	tctgctgaat	acaaacctgt	tcaagtatgtat	4740
ttcatctgta	ggggtaggg	ctgcttctt	aaatgcagtt	ttggcagctg	tggttgggt	4800
cattgtcata	agagttctta	tcgttggttc	tctctgtaca	catgtaaactg	tcaaaatatt	4860
atgaatggtt	tttatgctga	aagaagacat	cattggcaa	agagggctag	ggaatgaatt	4920
tagcacaaac	tcattttctt	ggagaccgtg	tatcatagtg	gtttttttt	tttttcttc	4980
tcttgttaaa	actgaacatt	atttctgc				5008

<210> SEQ ID NO 44

<211> LENGTH: 840

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 44

Met	Gly	Leu	Pro	Ser	Thr	Trp	Arg	Tyr	Gly	Arg	Gly	Pro	Gly	Ile	Gly
1						5			10			15			

Thr	Val	Thr	Met	Val	Ser	Trp	Gly	Arg	Phe	Ile	Cys	Leu	Val	Leu	Val
			20				25				30				

Thr	Met	Ala	Thr	Leu	Ser	Leu	Ala	Arg	Pro	Ser	Phe	Ser	Leu	Val	Glu
	35				40			45							

Asp	Thr	Thr	Leu	Glu	Pro	Glu	Glu	Pro	Pro	Thr	Lys	Tyr	Gln	Ile	Ser
	50				55			60							

Gln	Pro	Glu	Ala	Tyr	Val	Val	Ala	Pro	Gly	Glu	Ser	Leu	Glu	Leu	Gln
65				70			75		80						

Cys	Met	Leu	Lys	Asp	Ala	Ala	Val	Ile	Ser	Trp	Thr	Lys	Asp	Gly	Val
	85				90			95							

His	Leu	Gly	Pro	Asn	Asn	Arg	Thr	Val	Leu	Ile	Gly	Glu	Tyr	Leu	Gln
	100				105			110							

Ile	Lys	Gly	Ala	Thr	Pro	Arg	Asp	Ser	Gly	Leu	Tyr	Ala	Cys	Thr	Ala
	115				120			125							

-continued

Ala Arg Thr Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr
 130 135 140
 Asp Ala Ile Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Ser Ser Glu
 145 150 155 160
 Asp Val Val Ser Glu Asn Arg Ser Asn Gln Arg Ala Pro Tyr Trp Thr
 165 170 175
 Asn Thr Glu Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn
 180 185 190
 Thr Val Lys Phe Arg Cys Pro Ala Gly Gly Asn Pro Thr Pro Thr Met
 195 200 205
 Arg Trp Leu Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly
 210 215 220
 Gly Tyr Lys Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val
 225 230 235 240
 Val Pro Ser Asp Lys Gly Asn Tyr Thr Cys Leu Val Glu Asn Glu Tyr
 245 250 255
 Gly Ser Ile Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro
 260 265 270
 His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Thr Val
 275 280 285
 Val Gly Gly Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln
 290 295 300
 Pro His Ile Gln Trp Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr
 305 310 315 320
 Gly Pro Asp Gly Leu Pro Tyr Leu Lys Val Leu Lys Ala Ala Gly Val
 325 330 335
 Asn Thr Thr Asp Lys Glu Ile Glu Val Leu Tyr Ile Arg Asn Val Thr
 340 345 350
 Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly
 355 360 365
 Ile Ser Phe His Ser Ala Trp Leu Thr Val Leu Pro Ala Pro Val Arg
 370 375 380
 Glu Lys Glu Ile Thr Ala Ser Pro Asp Tyr Leu Glu Ile Ala Ile Tyr
 385 390 395 400
 Cys Ile Gly Val Phe Leu Ile Ala Cys Met Val Val Thr Val Ile Phe
 405 410 415
 Cys Arg Met Lys Thr Thr Lys Lys Pro Asp Phe Ser Ser Gln Pro
 420 425 430
 Ala Val His Lys Leu Thr Lys Arg Ile Pro Leu Arg Arg Gln Val Thr
 435 440 445
 Val Ser Ala Glu Ser Ser Ser Met Asn Ser Asn Thr Pro Leu Val
 450 455 460
 Arg Ile Thr Thr Arg Leu Ser Ser Thr Ala Asp Thr Pro Met Leu Ala
 465 470 475 480
 Gly Val Ser Glu Tyr Glu Leu Pro Glu Asp Pro Lys Trp Glu Phe Pro
 485 490 495
 Arg Asp Lys Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly
 500 505 510
 Gln Val Val Met Ala Glu Ala Val Gly Ile Asp Lys Asp Lys Pro Lys
 515 520 525
 Glu Ala Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Glu
 530 535 540

US 9,226,960 B2

155**156**

-continued

Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile
545 550 555 560

Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp
565 570 575

Gly Pro Leu Tyr Val Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg
580 585 590

Glu Tyr Leu Arg Ala Arg Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp
595 600 605

Ile Asn Arg Val Pro Glu Glu Gln Met Thr Phe Lys Asp Leu Val Ser
610 615 620

Cys Thr Tyr Gln Leu Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys
625 630 635 640

Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asn
645 650 655

Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Ile Asn Asn
660 665 670

Ile Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp
675 680 685

Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp
690 695 700

Val Trp Ser Phe Gly Val Leu Met Trp Glu Ile Phe Thr Leu Gly Gly
705 710 715 720

Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys
725 730 735

Glu Gly His Arg Met Asp Lys Pro Thr Asn Cys Thr Asn Glu Leu Tyr
740 745 750

Met Met Met Arg Asp Cys Trp His Ala Val Pro Ser Gln Arg Pro Thr
755 760 765

Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Ile Leu Thr Leu Thr Thr
770 775 780

Asn Glu Glu Tyr Leu Asp Leu Thr Gln Pro Leu Glu Gln Tyr Ser Pro
785 790 795 800

Ser Tyr Pro Asp Thr Arg Ser Ser Cys Ser Ser Gly Asp Asp Ser Val
805 810 815

Phe Ser Pro Asp Pro Met Pro Tyr Glu Pro Cys Leu Pro Gln Tyr Pro
820 825 830

His Ile Asn Gly Ser Val Lys Thr
835 840

<210> SEQ ID NO 45
<211> LENGTH: 5223
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 45

gatgtgcgga taagtacaat tacctattca cgtgttccct tcctaaagga gggtttccca 60
aacactcgtc ccctgtctat tgttcagagg aacaagacaa cgcaacatct cccacgaaca 120
tccgctgctt ccaccctcaa agcttcatga catgaaatgt ctggccccag tatgtgcag 180
acctattcta aggtgtctga agttgcacag cattctgtca tttgtttcct aacttgacat 240
aaaacaacgt aacgcattca ctgtgcacca aagctggcta ggaactgggg cagtggcgta 300
cagaggccgt tcaccaacag ggttccgaga ggtcatctgt gcacccctgc gggcagcgcg 360
gccccccccc tcgcctgcct ggccgggtgtc tctttgcggc tgctaggctt cgggggcagc 420

-continued

ggggggctcg ggactgcccc agcgcgaggc gctgattggc agagcgggcg ccgcgtcca	480
ggaaacggct cgggtttcag cggggggcgt gacccgcccc aggaggctgc ggccggcg	540
cggcgccgca ggggagagag cggggagagg cgagcggcgg cggccggcagg cgccgaacgg	600
gcccacggac gatcgaacgc gccgcgcaca gagctccggc gggggggctg cctgtgtt	660
cctggcccg cgtggcact gctctccggg ctggcgggg cgggcgtga gccccgggc	720
ctcagegttc ctgagcgtc cgagtgttca ctactcgcca gcaaagttt gagtaggca	780
cgccaaagctc cagtccttc ttctgctgtt gcccagatcc gagagcagct ccggtgtcat	840
gtccttagctg ttctgcgtc cccggcgcgc gtgaagcctc ggaaccttgg cgccggctgc	900
tacccaagga atcggtctt ttttgagtt ttctcccgag atcategcct gctccatccc	960
gatccactct gggctccggc gcagcacccg ggcagagggc ggcgtgcac tcaagtggca	1020
gccacacgcg cagcagcagc agcagtggga gcaggaacag cagtaacaac agcaacagca	1080
gcacagccgc ctcagagctt tggctcctga gccccctgtg ggctgaaggc attgcaggta	1140
gccccatggc tcagaagaag tgtgcagatg ggattaccgt ccacgtggag atatggaga	1200
ggaccaggga ttggcactgt gaccatggtc agctggggc gettcatctg cctggcttg	1260
gtcaccatgg caaccttgc cctggcccg ccctcctca gtttagttga ggataccact	1320
ttagaaccag aagagccacc aaccaaatac caaatctccc aaccagaagc gtacgtgtt	1380
gccccccggg aatcgctaga gttgcagtgc atgttgaag atgcccgcgt gatcgttgg	1440
actaaggat ggggtgcactt gggcccaac aataggacag tgcttattgg ggagtatctc	1500
cagataaaag gtgcccaccc tagagactcc ggcctctatg ctgtactgc agctaggacg	1560
gtagacagtg aaacttggta cttcatggtg aatgtcacag atgcccaccc atctggagat	1620
gatgaggacg acacagatag ctccgaagac gttgtcagtg agaacaggag caaccagaga	1680
gcaccgtact ggaccaacac cgagaagatg gagaagcggc tccacgtgt ccctggcc	1740
aacactgtga agttccgctg tccggctggg gggatccaa cggccacaat gaggtggta	1800
aaaaacggga aggagttaa gcaggagcat cgcattggag gctataaggt acgaaaccag	1860
cactgggcc ttattatgg aagtgtggtc ccgtcagaca aaggcaacta cacctgcctg	1920
gtggagaatg aatacgggtc catcaaccac acctaccacc tcatgtcgt tgaacggc	1980
ccacaccggc ccattctcca agctggactg cctgcaatg cttccacggt ggtcgagg	2040
gatgtggagt ttgtctgcaa ggttacagc gatgcccagc cccacatcca gtggatca	2100
cacgtggaaa agaacggcag taaatacggg cctgatgggc tgccctaccc caaggcctg	2160
aaggccggcgt gtgttaacac cacggacaaa gagattgagg ttctctatat tcgaaatgt	2220
acttttgggg atgtggggataatacgtgc ttggcggtt attctatcgg gatatccccc	2280
cactctgcat gtttgcact tctgccagcg cctgtgagag agaaggagat cacggctcc	2340
ccagattatc tggagatagc tatttactgc ataggggtct tcttaatcgc ctgcgtgt	2400
gtgacagtca tctttgccg aatgaagacc acgaccaaga agccagactt cagcagcag	2460
ccagctgtgc acaagctgac caagcgcaccc cccctgcggc gacaggtAAC agttcggcc	2520
gagtccagct cctccatgaa ctccaaacacc cccgtggta ggataacaac gcgtctgtcc	2580
tcaacagcgg acaccccgat gctagcagggt gtctccgagt atgagttgcc agaggatcca	2640
aagtggaaat tccccagaga taagctgacg ctggcAAAC ccctgggggaa aggttgc	2700
gggcaagtag tcatggctga agcagtggga atcgataaag acaaacccaa ggaggcgtc	2760
accgtggcag tgaagatgtt gaaagatgtt gcccacagaga aggacctgtc tgatctgt	2820

-continued

tca	gagatgg	agatgatgaa	gatgattggg	aaacataaga	acattatcaa	cctcctgggg	2880
gc	ctgcacgc	aggatggacc	tctctacgtc	atagttaaat	atgcatacgaa	aggcaacctc	2940
cgg	aaatacc	tccgagcccg	gaggccacct	ggcatggagt	actcctatga	cattaaccgt	3000
gt	ccccgagg	agcagatgac	cttcaaggac	ttggtgtcct	gcacctacca	gctggctaga	3060
gg	catggagt	acttggcttc	ccaaaaatgt	atccatcgag	atttggctgc	cagaaacgtg	3120
tt	ggtaacag	aaaacaatgt	gatgaagata	gcagacttg	gcctggccag	ggatatcaac	3180
a	acatagact	actataaaaa	gaccacaaat	gggcgacttc	cagtcaagt	gatggctcct	3240
ga	agccctt	ttgatagagt	ttcacatcat	cagagcgatg	tctggccctt	cgggggttta	3300
at	gtggaga	tcttacttt	agggggctea	ccctacccag	ggattcccgt	ggaggaactt	3360
tt	taagctgc	tcaaagaggg	acacaggatg	gacaagccca	ccaaactgcac	caatgaactg	3420
ta	catgatga	tgagggattg	ctggcatgtc	gtaccctcac	agagacccac	attcaagcag	3480
tt	ggtaacag	acttggatcg	aattctgact	ctcacaaccca	atgaggaata	cttggatctc	3540
ac	ccagcctc	tcgaacagta	ttctcttagt	taccccgaca	caaggagctc	ttgttctca	3600
gg	ggacgatt	ctgtgtttt	tccagacccc	atgccttatg	aacccctgtct	gcctcagtt	3660
cc	acacataa	acggcagtgt	taaaacatga	gtgaatgtgt	ttccctgtcc	ccaaacagga	3720
ca	gaccagg	aacctactta	cactgagcag	agaggctgt	cctccagagc	ctgtgacacg	3780
c	cctccactt	tatataatgga	tcagaggagt	aaatagtggg	aagcatattt	gtcaegtg	3840
ta	aaagattt	taacatgg	aacatgttac	ctaaccagga	aaggaagact	gttctctgat	3900
a	agtggacag	ccgcaagcca	ccatgccacc	ctctctgacc	caccatgtat	gctggctgt	3960
c	cccagttt	actcaaggca	gacaggtt	ctgccttct	tgttaattt	gtaataattt	4020
g	agaagat	atgtcagcac	acacttacag	agcacaaacg	cagtatata	gtgctggat	4080
t	atgtaaata	tattcaatt	atgtataat	atataattata	tatttacaag	gaatttattt	4140
t	tgttattgat	tttaatgg	tgtctctgat	cacctagaaa	attggctct	cttttttttta	4200
a	atagatatt	tgctaaatgc	tgttctttaga	gtttcttaat	tttcacccgag	cagaggtgg	4260
aa	aaatacttt	tgcttcagg	gaaaatggtg	tcacattaat	ttattaacga	attggtaata	4320
t	acgaaacga	ttaatcatct	atagttttt	tttttttta	atthaagtgg	catttctatg	4380
c	aggcagcac	ggaggactag	ttaatctatt	gcttggactt	aactggttat	tggatccctt	4440
g	agaagagaa	atatttacga	tatatactacta	atttgggggg	aatgggtt	ttgatttatt	4500
a	tgtttcaaa	ctctgctgtc	cgatgagcat	gtctagacac	cctaattgccc	atgtttcaag	4560
a	aacactgtt	aactctgtca	ccccagggt	acaattaacc	agacttccca	agacaaatgg	4620
t	taccagcatc	ctcatccaa	gatgcctaa	tccacttctc	tggagaacag	acttccatgg	4680
c	aatgtatagc	agggtcctct	cgtccggcag	ctggcctct	gcccgggtt	cacattcatc	4740
g	acgtttgcct	tgcttctcag	tgagttttaa	taacagcttc	agattttca	gcaccaagag	4800
c	ccctttgggg	aatctccatc	ctctcgaaagg	atggcaaaag	cccagcatca	ttcggtttag	4860
c	gtctgggac	tccttccat	cttcttaagg	gtttgctct	ggcttctacc	cacttctgac	4920
t	aagacctcac	ctcacaaaaa	gatctggct	aatagctaca	tccgacaaga	taacgcttat	4980
t	ttttgattt	cgtattcaag	tattttttt	cttggat	gcccactcac	tttgcac	5040
t	tcatgcgaca	tgtatgcaga	ttacactgt	tttatgttt	ttggaaattgg	agaaagtatt	5100
t	taataaaacc	tgttaattt	tatactgaca	ataaaaaatgt	ttctacagat	attaatgtta	5160

US 9,226,960 B2

161

-continued

acaagacaaa ataaatgtca cgtagttat tttttaaaaa aaaaaaaaaa aaaaaaaaaa 5220

aaa 5223

<210> SEQ ID NO 46

<211> LENGTH: 800

<212> TYPE: PRT

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 46

Met	Val	Val	Pro	Ala	Cys	Val	Leu	Val	Phe	Cys	Val	Ala	Val	Val	Ala
1															
															5220

Gly	Ala	Thr	Ser	Glu	Pro	Pro	Gly	Pro	Glu	Gln	Arg	Val	Val	Arg	Arg
															5223
20															30

Ala	Ala	Glu	Val	Pro	Gly	Pro	Glu	Pro	Ser	Gln	Gln	Glu	Gln	Val	Ala
															5223
35															45

Phe	Gly	Ser	Gly	Asp	Thr	Val	Glu	Leu	Ser	Cys	His	Pro	Pro	Gly	Gly
															5223
50															60

Ala	Pro	Thr	Gly	Pro	Thr	Val	Trp	Ala	Lys	Asp	Gly	Thr	Gly	Leu	Val
															5223
65															80

Ala	Ser	His	Arg	Ile	Leu	Val	Gly	Pro	Gln	Arg	Leu	Gln	Val	Leu	Asn
															5223
85															95

Ala	Ser	His	Glu	Asp	Ala	Gly	Val	Tyr	Ser	Cys	Gln	His	Arg	Leu	Thr
															5223
100															110

Arg	Arg	Val	Leu	Cys	His	Phe	Ser	Val	Arg	Val	Thr	Asp	Ala	Pro	Ser
															5223
115															125

Ser	Gly	Asp	Asp	Glu	Asp	Gly	Glu	Asp	Val	Ala	Glu	Asp	Thr	Gly	Ala
															5223
130															140

Pro	Tyr	Trp	Thr	Arg	Pro	Glu	Arg	Met	Asp	Lys	Lys	Leu	Leu	Ala	Val
															5223
145															160

Pro	Ala	Ala	Asn	Thr	Val	Arg	Phe	Arg	Cys	Pro	Ala	Ala	Gly	Asn	Pro
															5223
165															175

Thr	Pro	Ser	Ile	Ser	Trp	Leu	Lys	Asn	Gly	Lys	Glu	Phe	Arg	Gly	Glu
															5223
180															190

His	Arg	Ile	Gly	Gly	Ile	Lys	Leu	Arg	His	Gln	Gln	Trp	Ser	Leu	Val
															5223
195															205

Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	Asn	Tyr	Thr	Cys	Val	Val
															5223
210															220

Glu	Asn	Lys	Phe	Gly	Ser	Ile	Arg	Gln	Thr	Tyr	Thr	Leu	Asp	Val	Leu
															5223
225															240

Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn
															5223
245															255

Gln	Thr	Ala	Ile	Leu	Gly	Ser	Asp	Val	Glu	Phe	His	Cys	Lys	Val	Tyr
															5223
260															270

Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Val	Glu	Val	Asn
															5223
275															285

Gly	Ser	Lys	Val	Gly	Pro	Asp	Gly	Thr	Pro	Tyr	Val	Thr	Val	Leu	Lys
															5223
290															300

Thr	Ala	Gly	Ala	Asn	Thr	Thr	Asp	Lys	Glu	Leu	Glu	Val	Leu	Ser	Leu
															5223
305															320

His	Asn	Val	Thr	Phe	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly
															5223
325															335

Asn	Ser	Ile	Gly	Phe	Ser	His	His	Ser	Ala	Trp	Leu	Val	Leu	Pro	
															5223
340															350

Ala Glu Glu Glu Leu Met Glu Thr Asp Glu Ala Gly Ser Val Tyr Ala

162

US 9,226,960 B2

163**164**

-continued

355

360

365

Gly Val Leu Ser Tyr Gly Val Val Phe Phe Leu Phe Ile Leu Val Val
 370 375 380

Ala Ala Val Ile Leu Cys Arg Leu Arg Ser Pro Pro Lys Lys Gly Leu
 385 390 395 400

Gly Ser Pro Thr Val His Lys Val Ser Arg Phe Pro Leu Lys Arg Gln
 405 410 415

Val Ser Leu Glu Ser Asn Ser Met Asn Ser Asn Thr Pro Leu Val
 420 425 430

Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly Pro Val Leu Ala Asn Val
 435 440 445

Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys Trp Glu Leu Ser Arg Thr
 450 455 460

Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val
 465 470 475 480

Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp Arg Thr Ala Lys Pro
 485 490 495

Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Asp Lys Asp
 500 505 510

Leu Ser Asp Leu Val Ser Glu Met Met Lys Met Ile Gly Lys
 515 520 525

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Gly Pro
 530 535 540

Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys Gly Asn Leu Arg Glu Phe
 545 550 555 560

Leu Arg Ala Arg Arg Pro Pro Gly Met Asp Tyr Ser Phe Asp Ala Cys
 565 570 575

Arg Leu Pro Glu Glu Gln Leu Thr Cys Lys Asp Leu Val Ser Cys Ala
 580 585 590

Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile
 595 600 605

His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val
 610 615 620

Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Val His Asn Leu Asp
 625 630 635 640

Tyr Tyr Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala
 645 650 655

Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp
 660 665 670

Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr Leu Gly Ser Pro
 675 680 685

Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly
 690 695 700

His Arg Met Asp Lys Pro Ala Ser Cys Thr His Asp Leu Tyr Met Ile
 705 710 715 720

Met Arg Glu Cys Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys
 725 730 735

Gln Leu Val Glu Asp Leu Asp Arg Ile Leu Thr Val Thr Ser Thr Asp
 740 745 750

Glu Tyr Leu Asp Leu Ser Val Pro Phe Glu Gln Tyr Ser Pro Gly Gly
 755 760 765

Gln Asp Thr Pro Ser Ser Ser Ser Gly Asp Asp Ser Val Phe Thr
 770 775 780

-continued

His	Asp	Leu	Leu	Pro	Pro	Gly	Pro	Pro	Ser	Asn	Gly	Gly	Pro	Arg	Thr
785				790			795				800				

<210> SEQ ID NO 47

<211> LENGTH: 4232

<212> TYPE: DNA

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 47

tccggggcgtg	gcgggagcac	cccccaaccc	ccggccgggc	tgctgegcgc	cgggcagccc	60
caggttcagtg	cactgtggca	gggggggtgg	cgggagcagc	tggcgccgtg	cgatccactc	120
cgggcgggggg	actcagtggt	gggcggccgg	ccactgggac	agaggagacc	ctggaaaagc	180
gggccgagag	acggagccgc	gctgtgtctcc	acagaggcg	tctcccacccg	gcgcggagc	240
cgggcggtgg	gggttgcagc	atgcccgcgc	gctgtgttgc	aggacgcgc	ggcccccgc	300
ctggagccat	ggttagtccc	gcctgcgtgc	tagtgttctg	cgtggcggtc	gtggctggag	360
ctacttcga	gcctctctgg	ccagagcagc	gagttgtcg	gagagccgca	gaggttccag	420
ggcctgaacc	tagccagcag	gagcagggtgg	ccttcggcag	tggggacacc	gtggagctga	480
gtgtccatcc	tcctggaggt	gccccacag	ggcccaacgg	ctgggctaag	gttgtacag	540
gtctgggtgc	ctcccaccgc	atcctggtgg	ggcctcagag	gctgcaagtg	ctaaatgcct	600
cccacgaaga	tgcaggggtc	tacagctgcc	agcacccgc	cactcggcgt	gtgctgtgcc	660
acttcagtgt	gcgtgtaaaca	gatgctccat	cctcaggaga	tgacgaagat	ggggaggacg	720
tggctgaaga	cacaggggct	ccttatttgg	ctcgcccgga	gcgaatggat	aagaaactgc	780
tggctgtgcc	agccgcaaacc	actgtccgct	tccgctgccc	agctgctggc	aaccctaccc	840
cctccatctc	ctggctgaag	aatggcaaag	aattccgagg	ggagcatcgc	attggggca	900
tcaagctccg	gcaccagcag	tggagcttgg	tcatggaaag	tgtggtaccc	tccgatcgt	960
gcaactatac	ctgtgttagt	gagaacaagt	ttggcagcat	ccggcagaca	tacacactgg	1020
atgtgctgga	gcgcgtccca	caccggccca	tcctgcaggc	tgggtgcgc	gccaaaccaga	1080
cagccattct	aggcagtgac	gtggagttcc	actgcaaggt	gtacagcgt	gcacagccac	1140
acatccagtg	gctgaagcac	gtggaaagtga	acggcagcaa	ggtgggcct	gacggcacgc	1200
cctacgtcac	tgtactcaag	actgcaggcg	ctaaccac	cgacaaggag	ctagaggttc	1260
tgtccttgca	caatgtcacc	tttgaggacg	cggggagta	cacctgcctg	gcggcaatt	1320
ctattgggtt	ttcccatcac	tctgcgtggc	tgggtggct	gccagctgag	gaggagctga	1380
tggaaactga	tgaggctggc	agcgtgtacg	caggcgtct	cagctacggg	gtggtcttct	1440
tcctcttcat	cctgggtggt	gcagctgtga	tactctgc	cctgcgcagt	cccccaaaga	1500
agggcttggg	ctcgccccacc	gtgcacaagg	tctctcg	cccgcttaag	cgacaggtgt	1560
ccttggaaatc	taactctct	atgaactcca	acacaccct	tgtccggatt	gccccgtgt	1620
cctcaggaga	aggctctgtt	ctggccaatg	tttctgaact	tgagctgc	gctgacc	1680
agtggggagct	atccaggacc	cggctgacac	ttggtaagcc	tcttggagaa	ggctgcttgc	1740
gacaggtgg	catggcagaa	gctattggca	tcgacaagg	ccgtactgc	aagcctgtca	1800
ccgtggccgt	gaagatgctg	aaagatgatg	cgactgacaa	ggacctgtcg	gacgtggat	1860
ctgagatgga	gatgatgaaa	atgattggca	agcacaagaa	catcattaac	ctgctgggg	1920
cgtgcacaca	gggtggggccc	ctgtatgtgc	tggtggagta	cgcagccaag	ggcaatctcc	1980
gggagttccct	tcggggcgggg	cggcctccag	gcatggacta	ctccttgc	gcctgcaggc	2040

tgccagagga acagtcacc tgcaaggatc tagtgtcctg tgccctaccag gtggcacggg 2100
 gcatgaaata cttggcttct cagaagtgtta ttcacagaga ctggcgctcc agaaaacgtcc 2160
 tggtgaccga ggacaatgtg atgaagattt cgactttgg cctggctcga gatgtgcaca 2220
 acctggacta ctacaagaag accacaaatg gccggctacc tgtgaagtgg atggcaccag 2280
 aggcctttt tgaccgagtc tacacccacc agagtgtat ttggctttt ggtgtccctc 2340
 tctgggatcttacgctg gggggctac cgtatccctgg catcccagtg gaagagcttt 2400
 tcaagctgtt gaaagagggc caccgcattt gcaagccagc cagctgcaca catgacctgt 2460
 acatgatcat gcgggaaatgt tggcatgcgg tgccttcaca gaggcccacc ttcaagcagt 2520
 tggtagagga tttagaccgc atccctactg tgacatcaac cgacgagttt ttggacctct 2580
 cctgtccgtt tgagcagttac tgcgcagggtt gcccaggacac gcttagctcc agctcgctcg 2640
 gagatgactc ggtgttccacc catgacctgc taccggccagg tccaccagg aacgggggac 2700
 ctccggacgtg aaggccaaac agtccccacag accaagcccc aggcaatgtt tacggggacc 2760
 ctggccogcc ctgctactgc ttgggtgcag tggaccctag ccagccagg gcaatggcc 2820
 aacagtagac aagacttccct gcggttttat ccttgcgtcc tgggtgcaga ggcccttgg 2880
 gaacatgcac tgctgttagag taatctctg actggccagg gocaggagca ccaaacaaga 2940
 atgtaaaggccccc cccaccctgt gcaaccctgg ggttctggcc ctctcatttc ccactgtac 3000
 ctccaggga ccattgtgga gagggttaga ctccatgtcc agagtggggcc ttggccctct 3060
 tggtgcccca agctgagccct acaggaggcc tctgtctgt gtggcaaaacc tctctccatc 3120
 atggcacctt gtgcctgggg gtgtcatgc tgcacatctc caggctgcct gcttccacc 3180
 ctggccctca gagacaaatt acgggtaccc gaaggggggg cataatgtt atcagaaagg 3240
 tttattccag agaaaaatgt acatttatataat aaatagatgt tggatgtatgat ataaatataat 3300
 acatacatat atataagaat atctatatgg aaaaaggcaaa agttgaggcc caagggagca 3360
 agataactcca tgggtctcac taggaaactg gcaagagcag gctgagaaggc aaggggcttt 3420
 tctggcacgg cagttttgtt tggactggac ctgtatattt gtaaagctat ttatcaaccc 3480
 ccagagcgcc agtccccgac cccaggttca tagcgtttag tccagggtt ttgcagccat 3540
 cttaagttgt aacttattaa cagggaaaga ggttcatgtt ggatttaggg aattgttag 3600
 aacgtgcgtc tggctccac caggctggcc gtggccctt ggcgttgaa tggctctcc 3660
 agtcagagct ggctccagggtt agcattttctt gttggcttgcctt gtcggggatt 3720
 agatttatataat aggaactttc tttaggatgtt gttaaaaat tttaaggtga actggatattt 3780
 ttccatcaga ttattctaataat tgctatgtat tccaggcagg agcctgtgcc cagggaaagg 3840
 ctggccctgc aagaaggttc agatgttaat agttatctgt tacaagtttata tctatctata 3900
 atttatttgat tttttacaag ttgtttgtt gtaggtttaa cacttcttat gcagtgcctc 3960
 tagactttta tagcctagac tgctacctt caaagcttgg gagaacgtgg tgaatgcaat 4020
 ttgttactt ttgtactgtc actggccctt aggcttgggtt ggctgtccct tgcctgtcaa 4080
 ccagcagggtt caggacagtgc gctcagggtt gctttcttgg ggcgttagcac atgggttgc 4140
 agcccacactt ggcagatgtt gttttgttaa cacaaccaac ttactttcca aaaaataaaag 4200
 agataactgg ttccaaaaaa aaaaaaaaaaa aa 4232

<210> SEQ_ID NO 48
 <211> LENGTH: 799
 <212> TYPE: PRT

US 9,226,960 B2

169

170

-continued

<213> ORGANISM: *Mus musculus*

<400> SEQUENCE: 48

Leu Ser Leu Glu Ala Ser Glu Glu Met Glu Gln Glu Pro Cys Leu Ala
20 25 30

Pro Ile Leu Glu Gln Gln Glu Gln Val Leu Thr Val Ala Leu Gly Gln
 35 40 45

Pro Val Arg Leu Cys Cys Gly Arg Thr Glu Arg Gly Arg His Trp Tyr
50 55 60

Lys Glu Gly Ser Arg Leu Ala Ser Ala Gly Arg Val Arg Gly Trp Arg
65 70 75 80

Gly Arg Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala Gly Arg Tyr
85 90 95

Leu Cys Leu Ala Arg Gly Ser Met Thr Val Val His Asn Leu Thr Leu
100 105 110

Leu Met Asp Asp Ser Leu Thr Ser Ile Ser Asn Asp Glu Asp Pro Lys
115 120 125

Thr Leu Ser Ser Ser Ser Ser Gly His Val Tyr Pro Gln Gln Ala Pro
130 135 140

Tyr Trp Thr His Pro Gln Arg Met Glu Lys Lys Leu His Ala Val Pro
145 150 155 160

Ala Gly Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly Asn Pro Met
165 170 175

Pro Thr Ile His Trp Leu Lys Asp Gly Gln Ala Phe His Gly Glu Asn
180 185 190

Arg Ile Gly Gly Ile Arg Leu Arg His Gln His Trp Ser Leu Val Met
165 265 365

Glu Ser Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys Leu Val Glu
210 215 220

Asn Ser Leu Gly Ser Ile Arg Tyr Ser Tyr Leu Leu Asp Val Leu Glu

Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Thr

Thr Ala Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys Val Tyr Ser

Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Val Val Ile Asn Gly

275 280 285
Ser Ser Phe Gly Ala Asp Gly Phe Pro Tyr Val Gln Val Leu Lys Thr

Thr Asn Ile Asn Ser Ser Glu Val Glu Val Leu Thr Leu Arg Asn Val

305 310 315 320
Ser-Ala-Glu-Ala-Ala-Glu-Glu-Tyr-Tyr-Cys-Lys-Ala-Glu-Ala-Ser-Ile

325 330 335

Gly Leu Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro Glu Glu Asp

Leu Thr Trp Thr Thr Ala Thr Pro Glu Ala Arg Tyr Thr Asp Ile Ile

355 360 365

370 375 380

385 390 395 400

-continued

Val Thr Ile Gln Lys Leu Ser Arg Phe Pro Leu Ala Arg Gln Phe Ser
405 410 415

Leu Glu Ser Arg Ser Ser Gly Lys Ser Ser Leu Ser Leu Val Arg Gly
420 425 430

Val Arg Leu Ser Ser Ser Gly Pro Pro Leu Leu Thr Gly Leu Val Asn
435 440 445

Leu Asp Leu Pro Leu Asp Pro Leu Trp Glu Phe Pro Arg Asp Arg Leu
450 455 460

Val Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val Val Arg
465 470 475 480

Ala Glu Ala Phe Gly Met Asp Pro Ser Arg Pro Asp Gln Thr Ser Thr
485 490 495

Val Ala Val Lys Met Leu Lys Asp Asn Ala Ser Asp Lys Asp Leu Ala
500 505 510

Asp Leu Val Ser Glu Met Glu Val Met Lys Leu Ile Gly Arg His Lys
515 520 525

Asn Ile Ile Asn Leu Leu Gly Val Cys Thr Gln Glu Gly Pro Leu Tyr
530 535 540

Val Ile Val Glu Cys Ala Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg
545 550 555 560

Ala Arg Arg Pro Pro Gly Pro Asp Leu Ser Pro Asp Gly Pro Arg Ser
565 570 575

Ser Glu Gly Pro Leu Ser Phe Pro Ala Leu Val Ser Cys Ala Tyr Gln
580 585 590

Val Ala Arg Gly Met Gln Tyr Leu Glu Ser Arg Lys Cys Ile His Arg
595 600 605

Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asp Val Met Lys
610 615 620

Ile Ala Asp Phe Gly Leu Ala Arg Gly Val His His Ile Asp Tyr Tyr
625 630 635 640

Lys Lys Thr Ser Asn Gly Arg Leu Pro Val Lys Trp Met Ala Pro Glu
645 650 655

Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp Ser Phe
660 665 670

Gly Ile Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro
675 680 685

Gly Ile Pro Val Glu Glu Leu Phe Ser Leu Leu Arg Glu Gly His Arg
690 695 700

Met Glu Arg Pro Pro Asn Cys Pro Ser Glu Leu Tyr Gly Leu Met Arg
705 710 715 720

Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu
725 730 735

Val Glu Ala Leu Asp Lys Val Leu Leu Ala Val Ser Glu Glu Tyr Leu
740 745 750

Asp Leu Arg Leu Thr Phe Gly Pro Phe Ser Pro Ser Asn Gly Asp Ala
755 760 765

Ser Ser Thr Cys Ser Ser Ser Asp Ser Val Phe Ser His Asp Pro Leu
770 775 780

Pro Leu Glu Pro Ser Pro Phe Pro Phe Ser Asp Ser Gln Thr Thr
785 790 795

<210> SEQ ID NO 49
<211> LENGTH: 3146
<212> TYPE: DNA

-continued

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 49

gacatttcgt gctttcgcc	ccggggcggg	ggagctccgg	gccccgtgagt	gtgccagccc	60	
tgcgggatc	gtgaccggcg	cgcgcgggag	ccggggcggg	gaggagccag	gaaggtggc	120
agtggaaagt	ctggccctga	tcttgagatc	agcttggaa	aatgtggct	gctttggcc	180
ctgttgagca	tctttcaggg	gacaccagct	ttgtcccttg	aggcctctga	ggaaatggag	240
caggagccct	gccttagcccc	aatctggag	cagcaagagc	aggtgttgc	ggtggccctg	300
ggcagccctg	tgaggctgt	ctgtgggccc	accgagcggt	gtcgtaactg	gtacaaagag	360
ggcagccgccc	tagcatctgc	tgggcgagta	cgggggttgg	gaggccgcct	ggagatcgcc	420
agcttccttc	ctgaggatgc	tggccgatac	ctctgcctgg	cccggtggctc	catgaccgtc	480
gtacacaatc	ttacgttgc	tatggatgc	tccttaacct	ccatcagtaa	tgtgaagac	540
cccaagacac	tcaagcagctc	ctcgagtggt	catgtctacc	cacagcaagc	accctactgg	600
acacacaccccc	aacgcgttgc	gaagaaaactg	catgcagtgc	ctgccccggaa	tactgtcaaa	660
ttccgcgtgc	cagctgcagg	gaaccccatg	cctaccatcc	actggctcaa	ggatggacag	720
gccttcacag	gggagaatcg	tattggaggg	attcggctgc	gccaccaaca	ctggagcctg	780
gtgatggaaa	gtgtggtacc	ctcggaccgt	ggcacataca	catgccttgt	ggagaactct	840
ctgggttagca	ttcgcgtacag	ctatctccgt	gatgtgttgc	agcggtcccc	gcaccggccc	900
atcctgcagg	cggggttccc	agccaacacc	acagctgtgg	ttggcagcga	tgtggagcta	960
ctctgcgttgc	tgtacagcga	cgcgcggccc	cacatacagt	ggctgaaaca	cgtcgatc	1020
aacggcagca	gttcggcgc	cgacggtttc	ccctacgtac	aagtccctgaa	gacaacagac	1080
atcaatagct	cgaggataga	ggttttgtat	ctgagggaa	tgtccgttgc	ggatgcagga	1140
gagtttttttt	gtctgggggg	caactccatc	ggcccttcct	accagtcagc	gtggctcact	1200
gtgctgttgc	aggaagacct	cacgtggaca	acagcaaccc	ctgaggccag	atacagat	1260
atcatcttgt	atgtatcagg	ctcaactggtt	ctgtttgtc	tctgtgtct	ggccgggggt	1320
tatcatggc	aagtcatccg	tggccactac	tctcgccagc	ctgtcaactat	acaaaagctg	1380
tcccgtttcc	ttttggcccg	acagttctct	ttggagtcg	ggtcctctgg	caagtcaagt	1440
ttgtccctgg	tgcgagggt	ccgtctctcc	tccagcggcc	cgcccttgc	cacgggcctt	1500
gtgaatctag	acctgcctct	cgatccgtt	tggaaattcc	cccgggacag	gttgggtgc	1560
ggaaagcccc	tgggtgaggg	ctgtttttgg	caagtggttc	gtgcagaggc	ctttggatcg	1620
gatccctccc	ggcccgacca	aaccagcacc	gtggctgtga	agatgtgaa	agacaatgcc	1680
tccgacaagg	atttggcaga	cctggcttcc	gagatggagg	tgtgtgttgc	aatcgaaaga	1740
cacaagaaca	tcatcaacct	gctgggtgtc	tgcactcagg	aaggggccct	gtacgtgatt	1800
gtgaaatgt	ccgccaagggg	aaaccttcgg	gaattctcc	gtgccccggc	ccccccaggc	1860
cctgatctca	ccccctgtatgg	acctcgaggc	agcgaaggac	cactctccctt	cccgccctta	1920
gtctctgttgc	cctaccaggt	ggcccgaggc	atgcagttatc	tggagtctcg	gaagtgcac	1980
caccgggacc	tggctgtccc	aaatgtgtcg	gtgaccgagg	atgtatgtat	gaagatcgct	2040
gactttgggc	tggcacgtgg	tgtccaccac	attgactact	ataagaaaac	cagcaacggc	2100
cgccctgcac	tcaaatggat	ggtcccgag	gcattgttc	accgcgtgt	cacacaccag	2160
agtgacgtgt	ggtctttcg	gatctgtcg	tggaaatct	tcaccctcg	gggcctccca	2220
taccctggca	ttccggtgg	ggagctttcc	tcactgtgc	gagaggggca	caggatggag	2280

-continued

cggcccccaa	actgcccctc	agagctgtat	gggctaata	gggagtgc	gcacgcagcc	2340
ccatctcaga	ggcctacttt	taagcagctg	gtggaaagctc	tggacaagg	cctgctggct	2400
gtctctgaag	agtacattga	cctccgcctg	acctttggac	cctttctcc	ctccaatggg	2460
gatgccagca	gcacctgctc	ctccagtgac	tcgggtttca	gccacgaccc	tttgcctc	2520
gagccaagcc	cctccctt	ctctgactcg	cagacgacat	gagccggg	gcagcaatgt	2580
tgtatggct	acgcggccca	tggccgtggg	tctcctcgct	gagctgcaac	ctgatgcac	2640
gacatataat	gttggcagt	tcaggcctt	gacttgagac	tactgtgtc	gcagatcctc	2700
tctctggccc	tgtttgggg	agggccattc	ttggctctaa	ggttcatagt	tgaggccctc	2760
tgtccagcc	ttatgtccc	atctcagagt	tcaactctca	tctcaagatc	atggccttgc	2820
ccttggactc	atcctcagag	aagttaaagca	ttaaggcctt	ggcacgcagc	ctccgtctcc	2880
ggggctctcc	gggactagct	gcaaaactta	tgctctaaac	atttcttagt	cccccaaaca	2940
acctagaggc	cttgggactt	cacatcccc	agcacacaag	cctcaccacc	ccctgcctac	3000
ccccctccat	tgcttgttcc	agcatcttgg	tgaaaggggc	atcagctctg	gtgtccctga	3060
gagacgagaa	gcctgtggg	acgacagaag	aacatggcat	ttttataaat	tatTTTTT	3120
aaataaatct	ctgtgtgcct	ggtggc				3146

<210> SEQ ID NO 50

<211> LENGTH: 158

<212> TYPE: PRT

<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 50

Met	Ala	Ala	Gly	Ala	Ala	Gly	Ser	Ile	Thr	Thr	Leu	Pro	Ala	Leu	Pro
1								5			10			15	

Asp	Asp	Gly	Gly	Gly	Ala	Phe	Pro	Pro	Gly	His	Phe	Lys	Asp	Pro
					20			25			30			

Lys	Arg	Leu	Tyr	Cys	Lys	Asn	Gly	Gly	Phe	Phe	Leu	Arg	Ile	Asn	Pro
					35			40			45				

Asp	Gly	Arg	Val	Asp	Gly	Val	Arg	Glu	Lys	Ser	Asp	Pro	His	Ile	Lys
				50			55		60						

Leu	Gln	Leu	Gln	Ala	Glu	Glu	Arg	Gly	Val	Val	Ser	Ile	Lys	Gly	Val
65					70				75				80		

Ser	Ala	Asn	Arg	Phe	Leu	Ala	Met	Lys	Glu	Asp	Gly	Arg	Leu	Leu	Ala
					85			90				95			

Leu	Lys	Cys	Ala	Thr	Glu	Glu	Cys	Phe	Phe	Glu	Arg	Leu	Glu	Ser
					100			105			110			

Asn	Asn	Tyr	Asn	Thr	Tyr	Arg	Ser	Arg	Lys	Tyr	Ser	Asp	Trp	Tyr	Val
					115			120			125				

Ala	Leu	Lys	Arg	Thr	Gly	Gln	Tyr	Lys	Pro	Gly	Pro	Lys	Thr	Gly	Pro
					130			135			140				

Gly	Gln	Lys	Ala	Ile	Leu	Phe	Leu	Pro	Met	Ser	Ala	Lys	Ser
145							150				155		

<210> SEQ ID NO 51

<211> LENGTH: 574

<212> TYPE: DNA

<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 51

gaggctggac ggccggggca gggggcgagc cggccggcg ctggccggcg cggccggcg 60

-continued

ggggccgggg	cggcggggag	ccggccgggc	ccggcgcatg	gccccgggg	ccccggggag	120
catcaccacg	ctgcggggc	tgcggcga	ccccggggc	ggcgctttc	ccccggggca	180
cttcaaggac	cccaagcggc	tctactgcaa	gaacggcggc	ttcttctgc	gcatcaaccc	240
cgacggcagg	gtggacggcg	tccgcgagaa	gagcgatccg	cacatcaa	ac tgca gcttca	300
agcagaagaa	agaggagtag	tatcaatcaa	aggcgtta	gcaaaaccgt	ttctggctat	360
gaaggaggat	ggcagattgc	tggcactgaa	atgtgcaaca	gaggaatgtt	tcttttcga	420
gcgcttggaa	tctaataact	ataaacactta	ccggtcacgg	aagtactctg	attggtatgt	480
ggcactgaaa	aggactggac	agtacaagcc	cggaccaaaa	actggacctg	gacagaaagc	540
tatcctttt	cttccaatgt	ctgctaaaag	ctga			574

<210> SEQ_ID NO 52

<211> LENGTH: 819

<212> TYPE: PRT

<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 52

Met	Phe	Thr	Trp	Arg	Cys	Leu	Ile	Leu	Trp	Ala	Val	Leu	Val	Thr	Ala
1						5		10				15			

Thr	Leu	Ser	Ala	Ala	Arg	Pro	Ala	Pro	Thr	Leu	Pro	Asp	Gln	Ala	Leu
			20					25				30			

Pro	Lys	Ala	Asn	Ile	Glu	Val	Glu	Ser	His	Ser	Ala	His	Pro	Gly	Asp
	35				40				45						

Leu	Leu	Gln	Leu	Arg	Cys	Arg	Leu	Arg	Asp	Asp	Val	Gln	Ser	Ile	Asn
	50				55			60							

Trp	Val	Arg	Asp	Gly	Val	Gln	Leu	Pro	Glu	Asn	Asn	Arg	Thr	Arg	Ile
65					70			75				80			

Thr	Gly	Glu	Glu	Val	Glu	Val	Arg	Asp	Ala	Val	Pro	Glu	Asp	Ser	Gly
	85				90				95						

Leu	Tyr	Ala	Cys	Met	Thr	Asn	Ser	Pro	Ser	Gly	Ser	Glu	Thr	Thr	Tyr
	100					105				110					

Phe	Ser	Val	Asn	Val	Ser	Asp	Ala	Leu	Pro	Ser	Ala	Glu	Asp	Asp	Asp
	115				120			125							

Asp	Glu	Asp	Asp	Ser	Ser	Ser	Glu	Glu	Lys	Glu	Ala	Asp	Asn	Thr	Lys
	130				135			140							

Pro	Asn	Gln	Ala	Val	Ala	Pro	Tyr	Trp	Thr	Tyr	Pro	Glu	Lys	Met	Glu
145					150			155			160				

Lys	Lys	Leu	His	Ala	Val	Pro	Ala	Ala	Lys	Thr	Val	Lys	Phe	Lys	Cys
	165				170			175							

Pro	Ser	Gly	Gly	Thr	Pro	Asn	Pro	Thr	Leu	Arg	Trp	Leu	Lys	Asn	Gly
	180				185				190						

Lys	Glu	Phe	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val	Arg	Tyr
	195				200			205							

Ala	Thr	Trp	Ser	Ile	Ile	Met	Asp	Ser	Val	Val	Pro	Ser	Asp	Lys	Gly
	210				215			220							

Asn	Tyr	Thr	Cys	Ile	Val	Glu	Asn	Lys	Tyr	Gly	Ser	Ile	Asn	His	Thr
225					230			235			240				

Tyr	Gln	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln
	245				250			255							

Ala	Gly	Leu	Pro	Ala	Asn	Lys	Thr	Val	Ala	Leu	Gly	Ser	Asn	Val	Glu
	260				265			270							

Phe	Val	Cys	Lys	Val	Tyr	Ser	Asp	Pro	Gln	Pro	His	Ile	Gln	Trp	Leu
	275				280			285							

-continued

Lys His Ile Glu Val Asn Gly Ser Lys Ile Gly Pro Asp Asn Leu Pro
290 295 300

Tyr Val Gln Ile Leu Lys Thr Ala Gly Val Asn Thr Thr Asp Lys Glu
305 310 315 320

Met Glu Val Leu His Leu Arg Asn Val Ser Phe Glu Asp Ala Gly Glu
325 330 335

Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Ile Ser His His Ser Ala
340 345 350

Trp Leu Thr Val Leu Glu Ala Thr Glu Gln Ser Pro Ala Met Met Thr
355 360 365

Ser Pro Leu Tyr Leu Glu Ile Ile Tyr Cys Thr Gly Ala Phe Leu
370 375 380

Ile Ser Cys Met Val Val Thr Val Ile Ile Tyr Lys Met Lys Ser Thr
385 390 395 400

Thr Lys Lys Thr Asp Phe Asn Ser Gln Leu Ala Val His Lys Leu Ala
405 410 415

Lys Ser Ile Pro Leu Arg Arg Gln Val Thr Val Ser Ala Asp Ser Ser
420 425 430

Ser Ser Met Asn Ser Gly Val Met Leu Val Arg Pro Ser Arg Leu Ser
435 440 445

Ser Ser Gly Thr Pro Met Leu Ala Gly Val Ser Glu Tyr Glu Leu Pro
450 455 460

Glu Asp Pro Arg Trp Glu Leu Pro Arg Asp Arg Leu Ile Leu Gly Lys
465 470 475 480

Pro Leu Gly Glu Gly Cys Phe Gly Gln Val Val Leu Ala Glu Ala Ile
485 490 495

Gly Leu Asp Lys Asp Lys Pro Asn Arg Val Thr Lys Val Ala Val Lys
500 505 510

Met Leu Lys Ser Asp Ala Thr Glu Lys Asp Leu Ser Asp Leu Ile Ser
515 520 525

Glu Met Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn
530 535 540

Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu Tyr Val Ile Val Glu
545 550 555 560

Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu Gln Ala Arg Arg Pro
565 570 575

Pro Gly Met Glu Tyr Cys Tyr Asn Pro Thr Arg Ile Pro Glu Glu Gln
580 585 590

Leu Ser Phe Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly
595 600 605

Met Glu Tyr Leu Ala Ser Lys Lys Cys Ile His Arg Asp Leu Ala Ala
610 615 620

Arg Asn Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe
625 630 635 640

Gly Leu Ala Arg Asp Ile His His Ile Asp Tyr Tyr Lys Lys Thr Thr
645 650 655

Asn Gly Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp
660 665 670

Arg Ile Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu
675 680 685

Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Val Pro Val
690 695 700

-continued

Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro
705 710 715 720

Ser Asn Cys Thr Asn Glu Leu Tyr Met Met Arg Asp Cys Trp His
725 730 735

Ala Val Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu
740 745 750

Asp Arg Ile Val Ala Met Thr Ser Asn Gln Glu Tyr Leu Asp Leu Ser
755 760 765

Val Pro Leu Asp Gln Tyr Ser Pro Gly Phe Pro Ala Thr Arg Ser Ser
770 775 780

Thr Cys Ser Ser Gly Glu Asp Ser Val Phe Ser His Asp Pro Leu Pro
785 790 795 800

Asp Glu Pro Cys Leu Pro Arg Cys Pro Pro His Ser His Gly Ala Leu
805 810 815

Lys Arg His

<210> SEQ ID NO 53

<211> LENGTH: 2925

<212> TYPE: DNA

<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 53

cgcccccattgg	agggggcggtt	gagcgccatgc	gctgaggcagt	agccgcacca	gtggatgttt	60
tacacctggagg	tgcctcatcc	tttgggttgt	gctggtcaca	gcacgcgtgt	ctgctgccag	120
accggcccccc	acgctgcccc	accaagctct	gcccuaagcg	aacatcgagg	tggagtccca	180
ctcggegcac	cccgccgatc	tcctccagct	gctggccgg	ctgcgegatg	acgtgcagag	240
catcaactgg	gtgcgtgtat	gatgtcgatc	gcccagaac	aaccgcacgc	gcatcacccg	300
cgaggaggta	gaggtgcggg	acgggggtcc	cgaggactcg	gggctctatg	cctgcatacg	360
caacagcccc	tcggggagcg	agaccaccta	cttctccgtc	aacgtctcag	acgcactccc	420
ttctgcagag	gtatgtatgt	atgaagatga	ttcctccctcg	gaggagaagg	aggcggataaa	480
ccaacagccg	aaccaggctg	tagtcctta	ctggacctat	cccgagaaga	tggagaagaa	540
gctgcattcc	gtccccgctg	ccaaaacagt	gaaattcaag	tgccccctcg	gtgggacgccc	600
caaccccaacg	ctgcgtggc	tgaagaacgg	caaggagttc	aaggctgacc	accgcatacg	660
ggggtaacaag	gtccgcatacg	ccacctggag	catcatcatg	gactcggtgg	tgccatcaga	720
taagggcaac	tacacgtgca	tcgtggagaa	caaatacggg	agcatcaacc	acacatccca	780
gctggatgtc	gtggagcgct	ccccgcatacg	gcccatactcg	caggcagggc	tccccgc当地	840
ccaaacgggt	gcccctggca	gcaacgtgga	gtttgtctcg	aaggcttaca	gcaacccgca	900
gccccacatc	cagtggctga	aacacatcg	ggtgaacggc	agcaagatcg	gccccgacaa	960
cttgccttac	gtgcagatcc	tgaagacggc	tggcgatccaa	acgacagaca	aagagatggaa	1020
agtcccttac	ttaaggaatg	tctcatttgc	ggatgtctggg	gagttatacat	gtttggcgccc	1080
taattctatt	gggatctccc	atcaactctgc	atgggttgcaca	gttctcgaag	ctactgagca	1140
gtcaccagcc	atgtatgtat	ccccctcta	cctggagatc	atcaatcttac	gcacccggcgc	1200
cttccttac	tcctgcattgg	ttggtagact	catcatctac	aagatgaaga	gcaccaccaa	1260
gaagacagac	ttcaacagcc	agctggccgt	gcacaagctg	gcacaagagca	tcccactgc当地	1320
cagacaggtt	acagtgtcag	cagattccag	ctcctccatg	aactcggttg	tgtatgttgg	1380
gccccctca	cggtctccct	ccagcgaaac	ccccatgtcg	gcccggcgct	ccgagttatga	1440

-continued

gctggccgag	gacccgcgt	gggagctgcc	acgggacagg	ctgatectgg	gcaagccgt	1500
gggagaaggc	tgctttgggc	agggtgggtct	ggcgaggccc	atcgccctgg	acaaggacaa	1560
gcacaaaccgc	gtcaccaaag	tggctgtaaa	gatgctcaag	tccgatgcca	cagagaagga	1620
cctgtccgac	ctcatctccg	agatggagat	gatgaagatg	atcgcaagc	acaagaacat	1680
catcaacctg	ctgggtgcct	gcacgcagga	cggggccctc	tatgtcatcg	tggagtacgc	1740
cagcaaaggc	aacctgcgtg	agtacctgca	ggcacgcgc	ccacccggca	tggagttactg	1800
ctacaacccc	acacgcatcc	ccgaggagca	gtctcttcc	aaggacctgg	tgtctgtgc	1860
gtaccagggt	gcbcggcggca	tggagttacct	ggcctccaaa	aagtgcattc	acagggacact	1920
ggcggccagg	aacgtgctgg	tgaccgagga	caacgtgatg	aagatcgctg	acttcgggct	1980
ggcccgccgc	atccaccaca	tcgattacta	caagaagacg	acaaacggcc	gcttgcgggt	2040
gaagtggatg	gccccggagg	ctctgttca	ccgaatatac	acccatcaga	gtgatgtttg	2100
gtcggtcggt	gtgctgctgt	gggagatctt	cacgttgggt	ggttcgcctt	acccggcgt	2160
gcccgtggag	gagctttca	agctgctgaa	ggaaggccac	aggatggaca	agcccagcaa	2220
ctgcaccaac	gagctgtaca	tgtatgtcg	cgactgctgg	cacgcgtgc	cctccacagc	2280
ccccacccctc	aagcagctgg	tggaggacct	ggacaggatc	gtggccatga	cctccaatca	2340
ggagttacctg	gacctgtcgg	tgccgttgg	tcagttactcg	cccggttcc	cgccacgcg	2400
cagctccacc	tgctcctcgg	gggaggactc	ggtgttctcc	cacgaccgc	tgcccacgca	2460
gcccgtcctg	ccgcgtgcc	ccccgcacag	ccacggagcg	ctgaagcggc	actgaggctc	2520
cgcacgcgc	tgtgcccccc	cgggcaccac	cacgcgagg	aactgccc	agcttcggc	2580
tgtgttggg	ctgttggtcg	gtctttttt	tttatcaccc	atttaaaccc	ttcccacgag	2640
gtctgtgttt	ggacatcccc	acgtggcggt	gccgcgtgt	ccctatgggg	ccgatgcgcg	2700
ctgtgagcat	cgcatccag	cgctgcccc	acccacacgt	gtgggggtgt	cagcacacgg	2760
ggccgcggcc	gggatcagcg	ctaggacaga	agtcccgtgt	acatagctaa	aatatgtata	2820
aatatgaata	tatattaca	tgtctttta	aaagggtgg	taccagagct	gtgccaggct	2880
gggttagggag	gtgctgggt	ctggtagata	tcagttgtctat			2925

<210> SEQ ID NO 54

<211> LENGTH: 823

<212> TYPE: PRT

<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 54

Met	Val	Ser	Trp	Asp	Ser	Gly	Cys	Leu	Ile	Cys	Leu	Val	Val	Val	Thr
1								5		10		15			

Met	Ala	Gly	Leu	Ser	Leu	Ala	Arg	Pro	Ser	Phe	Asn	Leu	Val	Val	Glu
			20				25					30			

Asp	Ala	Thr	Leu	Glu	Pro	Glu	Glu	Pro	Pro	Thr	Lys	Tyr	Gln	Ile	Ser
			35				40				45				

Gln	Pro	Asp	Val	His	Ser	Ala	Leu	Pro	Gly	Glu	Pro	Leu	Glu	Leu	Arg
			50				55				60				

Cys	Gln	Leu	Lys	Asp	Ala	Val	Met	Ile	Ser	Trp	Thr	Lys	Asp	Gly	Val
			65			70			75			80			

Pro	Leu	Gly	Pro	Asp	Asn	Arg	Thr	Val	Ile	Ile	Gly	Glu	Tyr	Leu	Gln
			85			90						95			

Ile	Lys	Asp	Ala	Ser	Pro	Arg	Asp	Ser	Gly	Leu	Tyr	Ala	Cys	Thr	Ala
			100			105						110			

US 9,226,960 B2

185**186**

-continued

Ile Arg Thr Leu Asp Ser Asp Thr Leu Tyr Phe Ile Val Asn Val Thr
115 120 125

Asp Ala Leu Ser Ser Gly Asp Asp Glu Asp Asp Asn Asp Gly Ser Glu
130 135 140

Asp Phe Val Asn Asp Ser Asn Gln Met Arg Ala Pro Tyr Trp Thr His
145 150 155 160

Thr Asp Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr
165 170 175

Val Lys Phe Arg Cys Pro Ala Met Gly Asn Pro Thr Pro Thr Met Arg
180 185 190

Trp Leu Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly
195 200 205

Tyr Lys Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val
210 215 220

Pro Ser Asp Lys Gly Asn Tyr Thr Cys Ile Val Glu Asn Gln Tyr Gly
225 230 235 240

Ser Ile Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro His
245 250 255

Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Ala Val Val
260 265 270

Gly Gly Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro
275 280 285

His Ile Gln Trp Ile Lys His Val Glu Arg Asn Gly Ser Lys Tyr Gly
290 295 300

Pro Asp Gly Leu Pro Tyr Leu Gln Val Leu Lys Ala Ala Gly Val Asn
305 310 315 320

Thr Thr Asp Lys Glu Ile Glu Val Leu Tyr Ile Arg Asn Val Thr Phe
325 330 335

Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Ile
340 345 350

Ser Phe His Thr Ala Trp Leu Thr Val Leu Pro Ala Pro Glu Lys Glu
355 360 365

Lys Glu Phe Pro Thr Ser Pro Asp Tyr Leu Glu Ile Ala Ile Tyr Cys
370 375 380

Ile Gly Val Phe Leu Ile Ala Cys Met Val Leu Thr Val Ile Leu Cys
385 390 395 400

Arg Met Lys Asn Thr Thr Lys Lys Pro Asp Phe Ser Ser Gln Pro Ala
405 410 415

Val His Lys Leu Thr Lys Arg Ile Pro Leu Arg Arg Gln Val Thr Val
420 425 430

Ser Ala Asp Ser Ser Ser Met Asn Ser Asn Thr Pro Leu Val Arg
435 440 445

Ile Thr Thr Arg Leu Ser Ser Thr Ala Asp Ala Pro Met Leu Ala Gly
450 455 460

Val Ser Glu Tyr Glu Leu Pro Glu Asp Pro Lys Trp Glu Phe Pro Arg
465 470 475 480

Asp Lys Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln
485 490 495

Val Val Met Ala Glu Ala Val Gly Ile Asp Lys Asp Arg Pro Lys Glu
500 505 510

Ala Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Glu Lys
515 520 525

Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly

-continued

530	535	540
Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly		
545	550	555
560		
Pro Leu Tyr Val Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu		
565	570	575
Tyr Leu Arg Ala Arg Arg Pro Pro Gly Met Glu Tyr Ser Phe Asp Ile		
580	585	590
Asn Arg Val Pro Glu Glu Gln Met Thr Phe Lys Asp Leu Val Ser Cys		
595	600	605
Thr Tyr Gln Leu Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys		
610	615	620
Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asn Asn		
625	630	635
640		
Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Ile Asn Asn Ile		
645	650	655
Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met		
660	665	670
Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val		
675	680	685
Trp Ser Phe Gly Val Leu Met Trp Glu Ile Phe Thr Leu Gly Gly Ser		
690	695	700
Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu		
705	710	715
720		
Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr Asn Glu Leu Tyr Met		
725	730	735
Met Met Arg Asp Cys Trp Gln Ala Val Pro Ser Gln Arg Pro Thr Phe		
740	745	750
Lys Gln Leu Val Glu Asp Leu Asp Arg Ile Leu Thr Leu Thr Thr Asn		
755	760	765
Glu Glu Tyr Leu Asp Leu Ser Gly Pro Leu Glu Gln Tyr Ser Pro Ser		
770	775	780
Tyr Pro Asp Thr Arg Ser Ser Cys Ser Ser Gly Asp Asp Ser Val Phe		
785	790	795
800		
Ser Pro Asp Pro Met Pro Tyr Glu Pro Cys Leu Pro Lys Tyr Gln His		
805	810	815
Met Asn Gly Ser Val Lys Thr		
820		

<210> SEQ ID NO 55
<211> LENGTH: 2716
<212> TYPE: DNA
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 55

cgcgcggaaac	cctccggctg	cagccgctgc	cgttccccgt	gaggagggat	tgcctggcc	60
gaaggcactg	cgttctgtcc	atgctccctgt	agaggtgctc	agatggatt	aaagtccaca	120
tggagatatg	gaaatggacc	aggaacctac	tctaaaaaga	tggtcagctg	ggattcgggt	180
tgccttatct	gcctgggttgt	ggtcaccatg	gctggacttt	ccctggctcg	accgtcattt	240
aacttagttg	ttgaagatgc	cactttggaa	cccgaagagc	cgcaccaaccaa	ataccaaatc	300
tctcagccag	atgtacactc	tgcacttcca	ggagaaccac	ttgagttgcg	ctgtcaattg	360
aaagacgccg	tcatgatcag	ttggactaag	gatggggtcc	ccttggggcc	cgacaatagg	420
acagtgatta	ttggggagta	cttacaaatt	aaagatgctt	cacccagaga	ttcgggcctc	480

-continued

tatgcttgca ctgctttag gaccctagac agtgatactc tgtacttcat tgtaaatgtt	540
acagatgctc tttttctgg ggtatgtgaa gatgacaatg atgggtctga ggacttgc	600
aatgacacca accagatgag ggcccccata tggcacacaca cagacaaaat ggagaaaagg	660
ttacacgcag tgccagcage aaacactgtc aagtttcgtt gcccagccat gggaaaccca	720
acaccaacca tgagatggct gaaaaatggg aaagagtta aacaagaaca tcgtattggc	780
ggctataagg tccgcaacca gcactggagt ctcatcatgg agagcgtagt cccatccgac	840
aaagggaaatt acacgtgcat cgtggaaaac cagtatggct ccatcaacca cacttaccat	900
ctcgatgttgc tcgagcgtc accgcacagg cccatccctc aggctggcct tccagcaac	960
gectcggctg tagtcggagg ttagtgcgag tttgtctgca aagtctacag tgatgctcaa	1020
ccccacattc agtggataaa acacgttagag aggaatggca gttaatacgg accagatgga	1080
ctgccttacc ttcaagggtt aaaggctgcc ggtgttaaca ctacggacaa agaaattgag	1140
gttctctata tacggaatgt aactttttag gatgctgggg agtatacatg cttggcggtt	1200
aattctatttggatatccctt tcacactgca tgggtgacag ttctgcacgc ttctgaaaag	1260
gaaaaggaat ttcccacatc tccagactac ctggaaatag caatttactg cataggggtc	1320
ttcctgtatcg octgtatggt gctgacagtc atcctgtgcc goatgaagaa caccaccaag	1380
aaggcctgact tcagcagccca gcccgtgtc cacaagctga caaagcgaat ccctctgcgc	1440
agacaggtaa cagtgtcage tgactcaagc tcctccatga actccaacac gcctctgggt	1500
aggataacta cacgectctc ctccactgtc gatgccccaa tgctggcagg ggtctcgaa	1560
tatgaactgc cagaggatcc aaaatgggag tttccaagggtt ataagctgac gctgggtaaa	1620
ccccctggggg aaggctgctt tggcaagtg gtgtatggcgtt aagcgggtgg gattgacaaa	1680
gaccggccca aagaagcagt gactgtggca gtgaagatgc tgaaagatga tgctacggaa	1740
aaggatctat ccgacctggt gtcagagatg gagatgtatg agatgattgg gaaacataaa	1800
aatatcatca atcttcttgg agcctgtacc caggatggtc cgctgtatgtt gatgttagaa	1860
tatgcttcca aaggaaacct gcggtgatc ctgcgagcac gcccctcc tgggatggaa	1920
tactccttttgc atattaacag ggtcccagag ggcagatgtc cattcaagga ctggatcc	1980
tgcacgtacc agttggcaag aggcatggag tacttggctt cacaatgt tatccacca	2040
gacctagctg caagaaatgt tttggtaact gaaaataacg tcatgaaaat agcagacttc	2100
ggtttagcca gagacatcaa caaatatagat tattataaaa agactactaa tggacggctt	2160
ccagtaaagt ggtatggctcc agaagctctg tttgacagag tttacacaca ccaaagcgcac	2220
gtatggatcat ttggatgttgc aatgtggggat atcttccatgt taggaggatc gcccacccca	2280
ggaaatcccag tggaggact ttttaagctg cttaaagaag ggcaccgaat ggataaacct	2340
gccaactgca ccaatgact ctacatgtg atgagagatt gctggcaggc tgccttc	2400
caaagaccaa cttttaaaca gttggtagaa gacttggatc ggatccttac tctcacaact	2460
aacgaggagt atctggaccc tggcgacact ctggagcgtt attcacctag ctaccctgac	2520
accaggaggat cgtgttcttc aggtgtatgc tctgtttttt ctccatgtcc aatgcctt	2580
gaaccctgtc ttcccaagta ccaacacatg aatgggagcg ttaaaatgtt aaaaagaagca	2640
agaacatcaa gctacccatcc acatacagaa catctttctt ccggggaccctt aaagattctg	2700
cttgcatacata tgaaat	2716

-continued

```

<211> LENGTH: 827
<212> TYPE: PRT
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 56

Met Ser Ala Gly Gly Gly Ala Ala Ala Ala Ser Leu Pro Arg
1           5          10          15

Ser Arg Ala Gly Gly Met Arg Ala Ala Trp Gly Ser Val Trp Cys Leu
20          25          30

Cys Leu Ala Ala Ala Val Gly Ala Leu Pro Ala Ala Arg Arg Arg Gly
35          40          45

Ala Glu Arg Ser Gly Gly Gln Ala Ala Glu Tyr Leu Arg Ser Glu Thr
50          55          60

Ala Phe Leu Glu Glu Leu Val Phe Gly Ser Gly Asp Thr Ile Glu Leu
65          70          75          80

Ser Cys Asn Thr Gln Ser Ser Ser Val Ser Val Phe Trp Phe Lys Asp
85          90          95

Gly Ile Gly Ile Ala Pro Ser Asn Arg Thr His Ile Gly Gln Lys Leu
100         105         110

Leu Lys Ile Ile Asn Val Ser Tyr Asp Asp Ser Gly Leu Tyr Ser Cys
115         120         125

Lys Pro Arg His Ser Asn Glu Val Leu Gly Asn Phe Thr Val Arg Val
130         135         140

Thr Asp Ser Pro Ser Ser Gly Asp Asp Glu Asp Asp Asp Glu Ser
145         150         155         160

Glu Asp Thr Gly Val Pro Phe Trp Thr Arg Pro Asp Lys Met Glu Lys
165         170         175

Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys Pro
180         185         190

Ala Gly Gly Asn Pro Thr Pro Thr Ile Tyr Trp Leu Lys Asn Gly Lys
195         200         205

Glu Phe Lys Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His Gln
210         215         220

Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly Asn
225         230         235         240

Tyr Thr Cys Val Val Glu Asn Lys Tyr Gly Asn Ile Arg His Thr Tyr
245         250         255

Gln Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala
260         265         270

Gly Leu Pro Ala Asn Gln Thr Val Val Val Gly Ser Asn Val Glu Phe
275         280         285

His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu Lys
290         295         300

His Val Glu Val Asn Gly Ser Lys Tyr Gly Pro Asp Gly Thr Pro Tyr
305         310         315         320

Val Thr Val Leu Lys Thr Ala Gly Val Asn Thr Thr Asp Lys Glu Leu
325         330         335

Glu Ile Leu Tyr Leu Arg Asn Val Thr Phe Glu Asp Ala Gly Glu Tyr
340         345         350

Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala Trp
355         360         365

Leu Thr Val Leu Pro Ala Glu Glu Leu Met Glu Met Asp Asp Ser Gly
370         375         380

Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Thr Gly Leu Val Leu Phe

```

US 9,226,960 B2

193**194**

-continued

385	390	395	400
Ile Leu Val Leu Val Ile Val Ile Ile Cys Arg Met Lys Met Pro Asn			
405	410	415	
Lys Lys Ala Met Asn Thr Thr Thr Val Gln Lys Val Ser Lys Phe Pro			
420	425	430	
Leu Lys Arg Gln Gln Val Ser Leu Glu Ser Asn Ser Ser Met Asn Ser			
435	440	445	
Asn Thr Pro Leu Val Arg Ile Thr Arg Leu Ser Ser Ser Asp Gly Pro			
450	455	460	
Met Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Pro Asp Pro Lys Trp			
465	470	475	480
Glu Leu Ala Arg Ser Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly			
485	490	495	
Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys Asp			
500	505	510	
Lys Pro Asn Lys Ala Ile Thr Val Ala Val Lys Met Leu Lys Asp Asp			
515	520	525	
Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met Met			
530	535	540	
Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys			
545	550	555	560
Thr Gln Asp Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ser Lys Gly			
565	570	575	
Asn Leu Arg Glu Tyr Leu Arg Ala Arg Arg Pro Pro Gly Met Asp Tyr			
580	585	590	
Ser Phe Asp Thr Cys Lys Leu Pro Glu Glu Gln Leu Thr Phe Lys Asp			
595	600	605	
Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu Ala			
610	615	620	
Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu Val			
625	630	635	640
Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp			
645	650	655	
Val His Asn Ile Asp Tyr Tyr Lys Thr Thr Asn Gly Arg Leu Pro			
660	665	670	
Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His			
675	680	685	
Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Thr			
690	695	700	
Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Lys			
705	710	715	720
Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr His			
725	730	735	
Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Val Pro Ser Gln			
740	745	750	
Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu Thr			
755	760	765	
Met Thr Ser Thr Asp Glu Tyr Leu Asp Leu Ser Val Pro Phe Glu Gln			
770	775	780	
Tyr Ser Pro Ala Gly Gln Asp Thr His Ser Thr Cys Ser Ser Gly Asp			
785	790	795	800
Asp Ser Val Phe Ala His Asp Leu Leu Pro Asp Glu Pro Cys Leu Pro			
805	810	815	

-continued

Lys His Val Pro Cys Asn Gly Val Ile Arg Thr
820 825

<210> SEQ ID NO 57
<211> LENGTH: 5395
<212> TYPE: DNA
<213> ORGANISM: Gallus gallus
<400> SEQUENCE: 57

cgcagcagcg gagcggagcg ctgagcggcg gcagcatgct	60
ggcgccgggtt cggcgccggc ggcctcgct ccccgagcc ggcggggagg gatgcggcg	120
gcctggggct ccgtctgggt cctgtgcctg gcccggccg tcggagcgtt gccggcgcg	180
cgcggccgctt gagcggagcg gagcggcggtt caggcggcag aataactttag gagcggagacc	240
gcctttctgg aagagtttgtt gtttggaaatggta ttgaacttgc ctgttaacacc	300
cagagctctt ctgtgtcagt tttctgggtt aaagatggta ttgggatttc accttccaac	360
agaactcata ttggacaaaa actgttgaag ataatcaatg tgcataatg cgattcgggg	420
ctgtacagtt gcaagccaag gcattccaac gaggtcctgg gaaactttac agtcagatgt	480
acagattccc cttcgtcagg ttagtgcata gatgtgcac atgagtcaga ggatacagg	540
gtcccccttc ggacccggcc agataagatg gagaagaagc tgctggcagt tcctgcccc	600
aacaccgttc gcttccgatg tccagcagg gggaaacccaa ctccccaccat ttactggctg	660
aagaatggca aagaattcaa gggagagcac aggatcgggg gcatcaagtt ggcacacag	720
cagtggagct tgggtatggc gaggcgttgcc cctgcagatc gaggaaacta cacctgtgtt	780
gtggagaaca aatatggcaa tattaggcac acataccacg ttgtatgtttt agaacggta	840
ccccaccgcg caatcctgca agcaggactc cctgccaatc agactgttgtt ggtcgggagc	900
aatgtgaaat ttcaactgcaaa ggtctacagc gatgcccagc ctcatatcca gtggctgaaa	960
cacgtagaag tcaacggcag caagtatggc cctgatggaa caccctatgt cacagtgtt	1020
aagacggcag gtgttaacac aacggataag gagctagaga ttctgtactt gcgaaatgtt	1080
acttttggggat atgctggggat atatacttgtt ctcgcaggaa attcttatgg gttctcacat	1140
cactctgctt ggctgacggt gctaccagca gaggagctga tgggaaatggc tgattcgggc	1200
tcaatgtacg ctggcatttc cagctatggc actggcttag tcctcttcat cctgggtctg	1260
gtcattgtga ttatctgcag gatggaaatggc ccaaacaaaa aggccatgaa caccaccact	1320
gtacagaaatg tctccaaattt tccactcaag agacagcagg tgctgtggc gtccaaactct	1380
tccatgaattt ccaacacacc cctgggtccgg atcaactcgatc tctccctccag cgatggggcc	1440
atgctggcca acgtctctga gctggaaactt cctccagatc ccaagtggaa attggcacgt	1500
tctcgctga ccctggggaa gcccgttgggtt gaggagctgtt ttggccaatg ggtgatggcg	1560
gaagcaattt ggattgataa agacaagcca aacaaggccaa tcaaccgtggc tgcataatg	1620
ttaaaaatgtt atgccacaga caaggacattt tcagacatgg tctctgatgtt ggaaatgtt	1680
aaaatgtt ggaaggccaa aaacatcattt aacctgtctg cttgtgcac gcaaggacgg	1740
ccgctctacg tgggttgtt atatgcacatg aaggggaaactt tgcgggaaata cctcaggcga	1800
cgtcgcccac ctggcatggc ctattcccttc gacacatggc agctgcccga ggaggcagg	1860
acatttaaagt acctgggttcc ctggcctac caggtggccccc gggggcatggc gtactggcg	1920
tcacagaaat gcatatgc tgcattggca gccaggaaatg tgcataatg tgaggacaat	1980
gtgtatggaaa tagctgatgtt tggcattgtt agagacgttc acaacatcga ctattacaag	2040

-continued

aaaaccacca atggtcggct gcctgtgaaa tggatggctc cagaaggcatt gtttgcacgg	2100
gtctataactc accagagcga tgtctggctc tttggagtgc tactatggga gatcttcaact	2160
ttgggagggt ctccgtaccc gggaaattctt gttgaagaac tcttcaaact cttgaaagaa	2220
ggccatcgga tggataaaacc cgccaaactgt acccacgacc tgtacatgat catgcgggag	2280
tgctggcaacg ctgtccccctc gcagcgaccc acattcaagc agctggtgga agacctggac	2340
agagtcttca ccatgacatc cactgtatgag tacctggacc tctcggtgcc ctggagcaa	2400
tactcaccgg ctggccagga caccacacgc acctgctctt caggggacga ctgggtttt	2460
geacatgacc tgctgcctga tgacccctgc ctgcccaagc acgtgeccctg taatggcgctc	2520
atccgcacgt gacggccccc caggacacacg ggatggacag acaggcagtgt ttcccaccc	2580
ggcgcaagcg cagacgccc aagacaaacc catagtgaag gatgtttcca tgaaaactgct	2640
cggtgatgcc ggaggatttt tgttgtcaag ttttttttgg tttgtttgg ttgggttttt	2700
tcocatttgc tgtataaaaaa gtcaagaacg actgtttggc ctgaaggaac tcatacttttgc	2760
ccaaagatgat ctatcggtta tgatTTTTT tattattattt attattattt tttttttttt	2820
ttcctaagca gaatgttaaa cctggggta ctgcctccccc gctcgccctt gcccggcgcc	2880
tgagtagcca atctgtgcct actatatgaa aaagagggaa aaaatcttcc tagaagaaga	2940
aaagctaatg aaaaaaaaaa tgtaaagaat gtagaaatttcc ttgccttatg caatctgtac	3000
atgaacccccc ttggggagcc tgaaaagcca cgttgcctgc agggattcat atatttata	3060
aaatatatcat atttttgttgc tcgtcgcccccc tatagcttcg tgacccctt tcccgactac	3120
atagaaggaa tcttgtccag aagaagaaga aaaataaata aatgatacgc aaatcaacat	3180
ggagggaaataa taaaataaa aaaaaaaagac agtcaagtca tcctatagga	3240
ggagagcacc gcctggccgc tgccatgtc ctgttagggat tgcacacccca tggcatct	3300
tgagctgtgt cccagctgc aggaagagcc aatgtggggaa aatcttgc tttggagac	3360
gggggtttgc atactttgc ttacaaaggaa caagttgttag gggagaagct cctccagccc	3420
ttggcaccag cggtttggct ccatactcat gcagtgcactt ggagaaagaa gttacgggta	3480
cctgtaggca agagecttta acttataatca aaaaggttta ttccagagaa tctgtgtata	3540
tatctataaa tataatcctgt atatatataa ataaatataat gggaaaaaaa aaaaagaatg	3600
tataataacta attcaacgtt aagcagtact gagagagagt ctcaaaatc gaggattgtca	3660
atcttaggata tactgtatctg gatgaaagag aagagttgttgc tttgttttat atcttcacag	3720
ttttgtttta aaaattgtac gttAACATGT atattttgtaa agttattttat agacattaac	3780
agatctgttc ttcgggtttaa atagcgtac gttactgtaa actttaaatt tcaccgagtt	3840
taagggttgtt tttttttta acttataaa aatggagaaa aagtatattt atcaagtttt	3900
tcttttgtt ttagggaaa tattgaaaga atgtatagat gtacagtccct ttaacaaatt	3960
acatttaatg ttttatataat atatatataat atatatgtat tcgtaaaaaa aaatattgt	4020
ttatcctgga ttgcgttgag caaaggtaag tttatTTTAA aatacatcac cagtggtaa	4080
aacccaaacca atagcagaga gatggttttt acgtatttca gaaaaaaaaga gggccaagat	4140
ttcttcacactttaacca ctgtgcattt cggggggctg ggtgtttatt tttctatTTT	4200
ggaaatgaagg tattttttgtt ggtcgagtca ataagaagac cgcagcaaaag caacgtttg	4260
actttggatg acgcgcattttaat tttttttcccccgtgcc agtaatgttgc tttttgggt	4320
ttaagaaata ccatacgccc aaaatagaga gaggagcgcac attgtttgc gggagatgc	4380

-continued

aacgactgca tattttttt gcatttaaca cattaaaaaa tgccagtgtat gcctatgttt	4440
ctgtgttcga aatgtgtgc tttttttgtt cctgaatgtc agacagcaca tgagtaaaaa	4500
aagaaccctc acgtggctca ggctgacgag ggggggggagg ttgggggtgg gcttttttg	4560
tttgtgtttt ttcctttttt tttctttttt tttttttttt tttttttttg tccagaagac	4620
tgtatctact accacaaga ggcaaggaga attgcacccat gaattctcc tttatgttt	4680
gctctgggtgc atattacata tcaagggttc agaatagcag gatggcagca tctcattttt	4740
aagggtggttt gttttttttt tttttttttt ttttttttttct tcttagagcc aaaaaatct	4800
taccctaaaaaa taaaataattt atagtttgag gttatttcaa tggaagttt agaaggtaga	4860
tttctataga atttttttt gttgggattta aaaaaaaaaaag aaaaaaaaaaaga atttttttgg	4920
attttcttac aaatgtctgc taattgtgta cattccaagt actcgaagcg ttgcgtttcg	4980
tgtactgaaa aaagaaaatg tacaaaactg tgcatgatt caaatgttac tagatattat	5040
aaatatataat ataatttttatt gagtttttac aagatgtatc tgttgttagac ttgttgactt	5100
aacatttctt attcaatgt tatatagttt tatagcctgg actgttatct ttaagagett	5160
aaaaaaaaattha aaattccaat ttgttacat tttatactgt tgatgttaca atccacaggt	5220
ttgcgttagcg tgattttca acgagcaact ctgttcgat tattttataa atgtacttct	5280
gtgcctgaca gctgcagctg tccaaagggtgt gagacaaaca ctaaaataaaa ctattctgtct	5340
tttgtttaaaa aaaaaaaaaaaa aaaaaaaaaaaa aaaaaaaaaaaa aaaaaaaaaaaa aaaaaa	5395

What is claimed is:

1. A method for increasing endogenous antibody production in a mammal in need thereof and not in need of treatment for cancer, comprising:
 administering to a mammal in need of increased endogenous antibody production and not in need of treatment for cancer, a therapeutically effective amount of a compound selected from the group consisting of: ponatinib; N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,5-dimethylpiperazin-1-yl)benzamide; and
 35 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea,
 or a pharmaceutically-acceptable salt thereof.

2. The method of claim 1, wherein the mammal is a human.
 3. The method of claim 1, wherein the mammal is a geriatric human.
 4. The method of claim 1, wherein the mammal has an immune deficiency.
 5. The method of claim 4, wherein the mammal is a human.
 6. A method for increasing humoral immune response to vaccination with an immunogen in a mammal, comprising:
 40 in conjunction with the vaccination of a mammal to an immunogen, administering to the mammal a compound selected from the group consisting of: ponatinib;
 45 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea.
 11. The method of claim 1, wherein the compound is 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea.
 12. The method of claim 6, wherein the compound is N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,5-dimethylpiperazin-1-yl)benzamide.
 13. The method of claim 6, wherein the compound is 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea.